ANÆSTHESIA

VOLUME 16 · NUMBER 1 JANUARY 1961

THE ASSOCIATION OF ANÆSTHETISTS
OF GREAT BRITAIN & IRELAND

'Fluothane'

for Obstetric

Anaesthesia

* *Induction is rapid and smooth and is sufficient to allow application of forceps.*
* *There is a striking absence of reflex movement with manipulation under very light anaesthesia.*
* *Laryngospasm does not occur and there is no stimulation of salivary or bronchial secretions.*
* *Little tendency to vomiting and retching.*
* *Condition of the infant is satisfactory.*
* *Post-partum uterine atony and haemorrhage unlikely.*
* *Recovery is rapid without complications.*

'Fluothane' has been widely used in obstetric anaesthesia, for caesarian section, forceps delivery and for normal confinements. It presents useful advantages over other anaesthetic agents and has been described as the anaesthetic of choice for obstetrics. *

* *Canad. Anaes. Soc. J. (1960), 7, 109*

Fluothane – an I.C.I. discovery

(Halothane B.P.C.) Trade Mark

Literature and further information available on request.

FH80

IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION WILMSLOW CHESHIRE

ANÆSTHESIA

EDITORIAL BOARD

Chairman		R. P. W. SHACKLETON
Editor		C. LANGTON HEWER
Assistant Editors		J. ALFRED LEE · C. F. SCURR
Advisory Editor		JOHN GILLIES
Member		E. A. PASK*
The President of the Association	*ex officio*	RONALD JARMAN
Hon. Secretary of the Association	*ex officio*	H. J. V. MORTON*

Panel of Advisers JOHN BEARD · R. BRYCE-SMITH · P. CLIFFE
J. CLUTTON-BROCK · W. D. M. PATON · G. A. RAWLINS
J. D. ROBERTSON *Business Adviser* MAX PARRISH

*also member of Panel of Advisers

© Copyright 1961

THE ASSOCIATION OF ANÆSTHETISTS
OF GREAT BRITAIN & IRELAND
LONDON

'Fluothane' for Obstetric Anaesthesia

* *Induction is rapid and smooth and is sufficient to allow application of forceps.*
* *There is a striking absence of reflex movement with manipulation under very light anaesthesia.*
* *Laryngospasm does not occur and there is no stimulation of salivary or bronchial secretions.*
* *Little tendency to vomiting and retching.*
* *Condition of the infant is satisfactory.*
* *Post-partum uterine atony and haemorrhage unlikely.*
* *Recovery is rapid without complications.*

'Fluothane' has been widely used in obstetric anaesthesia, for caesarian section, forceps delivery and for normal confinements. It presents useful advantages over other anaesthetic agents and has been described as the anaesthetic of choice for obstetrics. *

* *Canad. Anaes. Soc. J. (1960), 7, 109*

Fluothane – an I.C.I. discovery

(Halothane B.P.C.) Trade Mark

Literature and further information available on request.

ICI

FH80

IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION WILMSLOW CHESHIRE

ANÆSTHESIA

EDITORIAL BOARD

Chairman		R. P. W. SHACKLETON
Editor		C. LANGTON HEWER
Assistant Editors		J. ALFRED LEE · C. F. SCURR
Advisory Editor		JOHN GILLIES
Member		E. A. PASK*
The President of the Association	*ex officio*	RONALD JARMAN
Hon. Secretary of the Association	*ex officio*	H. J. V. MORTON*

Panel of Advisers JOHN BEARD · R. BRYCE-SMITH · P. CLIFFE
J. CLUTTON-BROCK · W. D. M. PATON · G. A. RAWLINS
J. D. ROBERTSON *Business Adviser* MAX PARRISH

*also member of Panel of Advisers

© Copyright 1961

THE ASSOCIATION OF ANÆSTHETISTS
OF GREAT BRITAIN & IRELAND
LONDON

CONTENTS

Page

EDITORIAL 1

AN INVESTIGATION OF NEW FLUORINE COMPOUNDS IN ANÆSTHESIA (1)
T. H. S. Burns, J. M. Hall, A. Bracken, G. Gouldstone *and* D. S. Newland 3

AN INVESTIGATION OF NEW FLUORINE COMPOUNDS IN ANÆSTHESIA (2)
J. H. Glover *and* H. W. Hodgson 19

SERUM GLUTAMIC OXALACETIC ACID TRANSAMINASE ACTIVITY FOLLOWING HYPOTHERMIA ... ... Otto W. Wendel 24

THE EFFECT OF HALOTHANE (FLUOTHANE) ON THE THALAMUS AND MIDBRAIN RETICULAR FORMATION
S. Davis, E. Quitmeyer *and* W. F. Collins 32

THIOPENTONE AND METHOHEXITAL (A comparison as main anæsthetic agents for a standard operation) ... ... J. W. Dundee *and* J. Moore 50

PROMETHAZINE (Its influence on the course of thiopentone and methohexital anæsthesia) ... ... J. Moore *and* J. W. Dundee 61

PHENACTROPINIUM CHLORIDE (Clinical observations) D. W. Eyre-Walker 74

PAIN AND THE BARBITURATES ... ... J. Clutton-Brock 80

DECAMETHONIUM IN CLINICAL ANÆSTHESIA ... ... G. C. Fisk 89

SUMMARIES OF PAPERS READ AT THE ANNUAL GENERAL MEETING

The myth of phenothiazine potentiation J. W. Dundee *and* J. Moore 95

The Cardiff calculator for halothane in the closed circuit... S. Galloon 96

Respiratory insufficiency following anæsthesia for aortic embolectomy
J. I. Murray Lawson *and* R. D. M. Davie 97

Studies on the clinical and pathological effects of hydroxydione
J. D. Robertson 98

The tight brain ... ... J. D. Whitby 99

Numorphan, a new supplement to anæsthesia ... ... M. Swerdlow 101

NEW INVENTIONS

A drip epidural indicator ... ... Massey Dawkins 102

An apparatus for intravenous anæsthesia in the neonate
W. J. Thomson 104

ANÆSTHETIC LITERATURE 106

BOOK REVIEWS

Electroencephalography in anesthesiology
Albert Faulconer *and* Reginald G. Bickford 112

The pharmacology of anesthetic drugs ... ... John Adriani 112

Clinical applications of diagnostic and therapeutic nerve blocks
John J. Bonica 114

Illustrating medicine and surgery ... ... Margaret C. McLarty 114

Oxygénotherapie ... ... L. Binet *and* M. Bochet 114

CORRESPONDENCE

An unusual case of post-anæsthetic collapse ... J. M. Haughton 115

Bernard Johnson Memorial ... ... Geoffrey Organe 116

ASSOCIATION NEWS 117

FACULTY NEWS 121

COMMONWEALTH AND FOREIGN NEWS 122

Sofnol non-hygroscopic Soda-lime is used in leading London Hospitals and throughout the world for anaesthetic and metabolic apparatus.

SOFNOL

NON-HYGROSCOPIC
SODA-LIME

SOFNOL LTD., WESTCOMBE HILL, GREENWICH, LONDON, S.E.10

D/TAS/SL.324

The Journal of

The American Society of Anesthesiologists, Inc. . . .

ANESTHESIOLOGY

. . . is published bi-monthly

EDITORIAL BOARD

Editor

JAMES E. ECKENHOFF, M.D.

Associate Editors

JOHN ADRIANI, M.D.
STUART C. CULLEN, M.D.
STEVENS J. MARTIN, M.D.
JOHN W. PENDER, M.D.

and consists of original articles, both clinical and experimental; editorials; review articles; current comments; case reports; abstracts of the current literature, and book reviews.

NEW SUBSCRIPTIONS are entered to commence with the current issue, but single copies of back issues may be purchased for $2.00 each, if available. Present non-member subscription rate : $11.00 a year, including postage to your side of the Atlantic. Arrangements may be made through your bank for remittance in U.S. funds payable through a bank in the U.S. When completing the order form be sure that the name and address are legibly printed or typed.

.....

ANESTHESIOLOGY
Attention : Circulation Manager
3 PENN CENTER PLAZA PHILADELPHIA 2, Pa., U.S.A.

Please enter my subscription to ANESTHESIOLOGY, effective with the current issue, for which ( ) I am enclosing a draft for $11.00 in U.S. funds
( ) kindly send me your invoice

The Journal is to be addressed:

Name.....

Address.....

.....

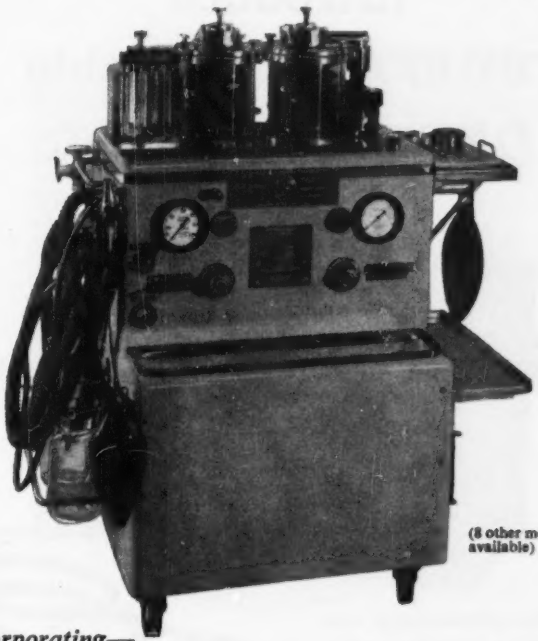
BLEASE OF LONDON

PRESENTS

THE LATEST

ALL PURPOSE 'PULMOFLATOR'

(Model P11) (REGD.)



(8 other models available)

Incorporating—

- Positive and negative phases, anæsthesia on all circuits, patient triggering and resuscitation using atmospheric air.
- This model having two "heads" enables an immediate change over to any circuit, by movement of one control.
- Triggering device can be used with a variable negative phase.
- Cycling of inflation by "pressure" and "volume".
- Large capacity pump unit with a variable control to ensure normal/rapid rate of inflation.

BLEASE ANÆSTHETIC EQUIPMENT LTD.

Makers and Suppliers of Mechanical Respirators, Resuscitation Apparatus, "Trilene" Inhalers, Gordh Needles, Blood Pressure Apparatus, Anæsthetic Apparatus, etc.

RYEFIELD CRESCENT, NORTHWOOD HILLS, MIDDLESEX

Tel.: NORTHWOOD 2413

ALLEN & HANBURYS LTD

introduce
THE SEALEY Portable
DEFIBRILLATOR

MODEL
P.D.2

—ready for immediate use
in cardiac emergencies

DESCRIPTIVE LITERATURE AVAILABLE ON REQUEST

NOTE: This Portable Defibrillator is only one of a comprehensive range of Sealey Electrical Cardiac Resuscitation Apparatus, including internal and external defibrillators and cardiac pacemakers.

SOLE WORLD DISTRIBUTORS

ALLEN & HANBURYS LTD (*Surgical Division*) LONDON E2

The . . .

MORTIMER RESPIRATOR

(Mk II)

NOW AVAILABLE AT - - **£49 - 10 - 0**

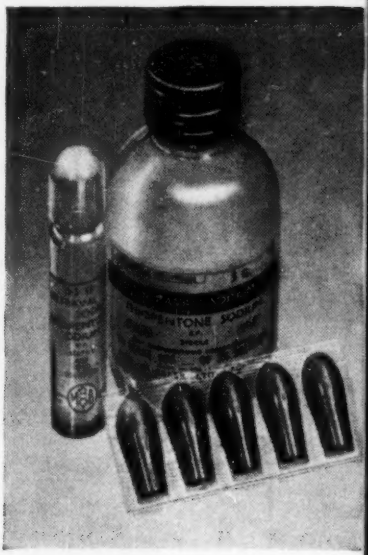
Further particulars from

COVENTRY & JEFFS LTD.

(Engineering Department)

STAFFORD ST., BEDMINSTER, BRISTOL, 3

Telephone 66 – 4661



for rapid induction and smooth recovery

'INTRAVAL' SODIUM

trade mark *brand*

THIOPENTONE SODIUM B.P.

The established intravenous agent available in presentations for 2·5 and 5 per cent solutions.

SUPPLIES

for the preparation of the 2·5 per cent solution:

Boxes of: 5 x 0·5 gramme ampoules
25 x 0·5 gramme ampoules
(with water for injection)

Multi-dose containers of 2·5 grammes
(without water for injection)

A suppository form is available for children.

Boxes of: 5 x 125 mg.
5 x 250 mg.
5 x 500 mg.
5 x 750 mg.

For the preparation of the 5 per cent solution:

Boxes of: 5 x 0·25 gramme ampoules
5 x 0·5 gramme ampoules
25 x 0·5 gramme ampoules
5 x 1 gramme ampoules
25 x 1 gramme ampoules
(with water for injection)

50 x 0·5 gramme and 50 x 1 gramme ampoules

Multi-dose containers of 5 grammes
(without water for injection)

for adequate muscle relaxation

'FLAXEDIL'
trade mark *brand*

GALLAMINE TRIETHIODIDE INJECTION B.P.

the relaxant with medium duration of action.

'BREVIDIL' M
trade mark *brand*

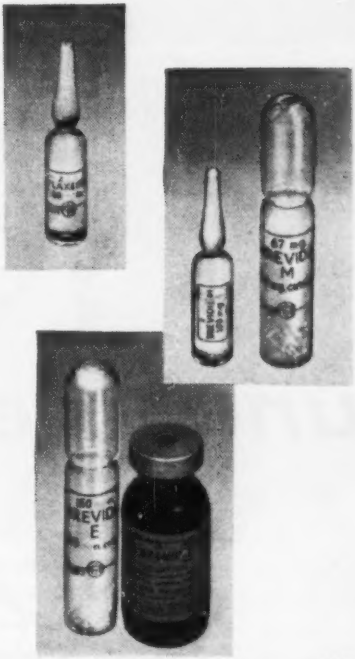
SUXAMETHONIUM PREPARATIONS

provides complete relaxation of short duration for intubation, orthopaedic manipulations, bronchoscopy, electro-convulsive therapy and dental surgery.

'BREVIDIL' E
trade mark *brand*

SUXETHONIUM BROMIDE

gives even shorter relaxation than suxamethonium with reduced incidence of muscular after-pains.



MA6950

SUPPLIES

'FLAXEDIL' solution

A 4 per cent solution in ampoules of 2 ml. and 3 ml., and multi-dose containers of 10 ml.

'BREVIDIL' M solution

2 ml. ampoules containing 100 mg. suxamethonium chloride and 10 ml. multi-dose containers containing 50 mg. suxamethonium chloride in each ml.

powder

Ampoules of 67 mg. suxamethonium bromide (40 mg. cation) and multi-dose containers of 335 mg. suxamethonium bromide (200 mg. cation).

'BREVIDIL' E powder

Ampoules of 150 mg. bromide (100 mg. cation) and multi-dose containers of 750 mg. (500 mg. cation).

solution

A 15 per cent solution in multi-dose containers of 10 ml. (each ml. contains 150 mg. suxethonium bromide, equivalent to 100 mg. cation).

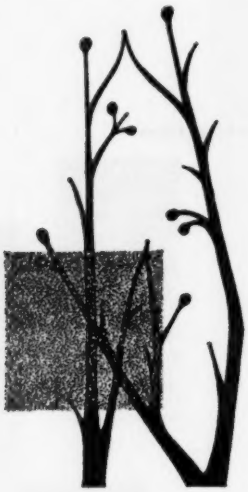
Detailed information is available on request

M&B *brand Medical Products*

Manufactured by

MAY & BAKER LTD

DISTRIBUTORS PHARMACEUTICAL SPECIALITIES (MAY & BAKER) LTD · DAGENHAM



duncaine*

brand Lignocaine

Since 1948 we have manufactured Lignocaine preparations and marketed them under the brand name 'Xylocaine'—under licence from A. B. Astra of Sweden. It has now been agreed by Astra and us that we shall cease to use the word 'Xylocaine' on 31 December 1960. We shall, however, continue to manufacture Lignocaine and its preparations but from 1 January 1961 we shall market them under our own brand name 'Duncaine'.

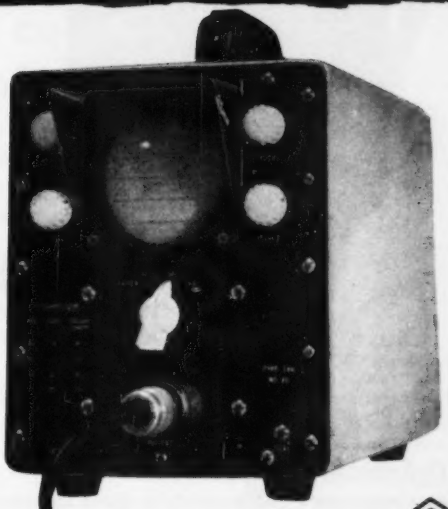
DUNCAN FLOCKHART OF EDINBURGH

The Doctors' House

* A registered trade mark, the property of
DUNCAN, FLOCKHART & CO LTD WHEATFIELD ROAD EDINBURGH 11
384

Presenting the

VIDEOGRAPH



Designed for routine monitoring of cardiac traces

Can be safely used in the presence of explosive gases

MEDICAL & INDUSTRIAL EQUIPMENT LTD.

SPECIALISTS IN ANAESTHETIC AND RESPIRATORY APPARATUS

10 & 12, NEW CAVENDISH STREET, LONDON, W.1.

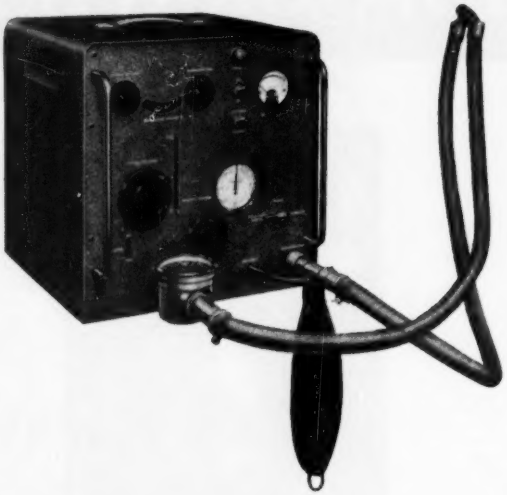
Telephone: WELBECK 1851 & 1504. *Telegrams: NARCOSIS, LONDON.*

MANCHESTER: 152-154 Oxford Road *Phone: Ardwick 5906*

TORONTO, CANADA: 83-85 Granville Street *Phone: Walnut 3-3845*

THE BARNET VENTILATOR

ENTIRELY NEW · VERSATILE · PORTABLE



Electronically time cycled.

Inspiratory and expiratory times independently adjustable from .5 to 4.5 seconds.

Electronic trigger actuated by suction of −1 cm. H_2O.

Time lapse between patient demand and operation of inspiratory bellows 0.2 second.

Continuously and independently variable positive and negative pressure controls.

Pressure range −10 to + 45 cm. H_2O.

Operation from built-in batteries for up to twenty hours.

Batteries recharged by connection to mains electricity supply.

Weight 56 lb.

For full details write to:-

W. WATSON & SONS LTD.

BARNET · HERTS

WINSTON INSTRUMENTS

THE BLOOD PRESSURE FOLLOWER

for the continuous recording of blood pressure

Records continuously the systolic blood-pressure in man over long periods of time without the need for arterial puncture. May be used in the routine recording of blood pressure, during and after operations, in drug response studies on hypertensive patients, in fact in all cases where more than an isolated reading of blood pressure is required.

In the interests of safety there is no electrical connection to the patient.

For fully descriptive literature, write to Dept. A

* *Console cabinet on castors with anti-static rubber tyres.*
* *Top case containing equipment has sloping instrument panel for easy operation and reading. Case is removable and can be used as a portable equipment.*
* *The bottom section of the console cabinet has a drawer in which the recorder is mounted.*
* *The blank panel below the Pen Recorder can be replaced by the high- and low-pressure warning and control panel.*

WINSTON
ELECTRONICS LIMITED
GOVETT AVENUE
SHEPPERTON
MIDDLESEX

Telephone: Walton-on-Thames 26321-6
Telegrams: Winston, Shepperton

CANADIAN ANÆSTHETISTS' SOCIETY JOURNAL

Editor

R. A. GORDON, C.D., B.SC., M.D., F.R.C.P.(C), F.F.A.R.C.S.

Editorial Board

ALAN B. NOBLE, M.D., F.A.C.A.
LOUIS LAMOUREUX, M.D.
E. A. GAIN, B.A., M.D.
LEON LONGTIN, M.D., F.R.C.P.(C)

The Journal is issued quarterly for Members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anæsthesia.

Annual Subscription $8.00 (£3 1s. 0d.) *post paid*

Through your Bookseller or

The Secretary
Canadian Anæsthetists' Society
178 St. George Street
Toronto 5, Ontario, Canada

The best of the current literature in brief . . .

Survey of Anesthesiology

Edited by C. Ronald Steven *First published 1957*

A bi-monthly survey of worldwide literature relating to anesthesiology, in succinct condensations to which are appended pithy editorial comments.
The logical solution to the doctor's dilemma of more and more literature and less and less time in which to read it. The fastest growing journal in the field.
Adds breadth of coverage to the depth you are now getting from the standard journals. Subscribe today!

Organized under the following headings

Editorial Pharmacology Physiology Biochemistry
Metabolism Techniques General anæsthesia
Spinal and regional anæsthesia Pediatric anæsthesia
Geriatric anæsthesia Preoperative care
Postoperative care Classical file

Published bi-monthly, one volume a year, by
THE WILLIAMS & WILKINS COMPANY
Baltimore, Maryland, U.S.A
Volume 5 current in 1961

Available in the United Kingdom from
Baillière, Tindall & Cox, Ltd
7 & 8 Henrietta St., Covent Garden, London, W C 2
Annual subscription £4 : 6 : 0 postage paid

NEW

PENTOTHAL

in disposable rectal syringe

A new dosage form of Pentothal is now available—Rectal Pentothal Suspension—supplied in a disposable syringe. This is a specially designed plastic syringe called the Abbo-Sert which is ready for immediate use. It is provided with two detachable rectal applicators. Rectal Pentothal Suspension in the Abbo-Sert offers significant advantages:

- **No necessity to prepare the drug.**
- **Smaller volume of drug.**
- **No need for bowel preparation.**
- **Obviates the need for buttock strapping.**
- **Absorption uniform.**
- **Onset of action gradual and consistent.**

Pentothal is the original form of Thiopentone Sodium B.P. and was developed by Abbott nearly 25 years ago.
New Rectal Suspension is a useful addition to the existing range of Pentothal dosage forms.

ABBOTT LABORATORIES LTD · LONDON · W.1

EDITORIAL

It is unfortunate that, while tremendous progress has been made in the cure of disease by medicine and surgery, there is a steadily increasing morbidity and mortality from other hazards, of which a large proportion can be included under the general term of 'accident'.

Much attention has been focussed of late on Accident Services, and an independent Review Committee has been set up under the chairmanship of Mr Osmond-Clarke, which has invited The Association of Anæsthetists of Great Britain and Ireland to appoint a representative. The Subcommittee on Accident Services of the Central Health Services Council, under the chairmanship of Sir Harry Platt, has also invited the Association to give evidence before it. Thus, it is encouraging to note, that the vital role played by anæsthetists in the treatment of accident patients has been recognised by the authorities and, in fact, practically all the 'crash teams', organised by hospitals, include an anæsthetist as an essential member. It is not always realised, however, that an *experienced* person is necessary for such work as special problems are involved. For instance, many victims of accidents have full stomachs, while delayed emptying is common after shock so that inhalation of gastric contents is a real risk. Again, shocked patients have a poor peripheral circulation and the usual hypodermic injection of morphine has little result at the time, but a most profound one when restorative measures become effective. Furthermore, patients in shock are extremely susceptible to potent anæsthetics, particularly when given by the intravenous route, a fact made perfectly clear to anæsthetists dealing with air raid casualties during the last war. The

ever increasing number of road accidents includes head injuries with patients in partial coma, facio-maxillary trauma with debris in the mouth and pharynx and 'stove-in' chests, with the complications of pneumothorax and paradoxical respiration. It is obvious that the duty anæsthetist must have had experience with all these conditions and must be competent, if required, to undertake the exacting responsibility for post-operative care.

For these, and many other reasons, readers are urged to use whatever influence they may possess, to ensure that anæsthetists are represented at any discussion on Accident Services. Senior consultants also have a moral duty to arrange that an experienced anæsthetist is included in any team detailed to cope with an 'incident' either at the site of disaster or in hospital.

An investigation of new fluorine compounds in anæsthesia (1)

T. H. S. BURNS, MA, BM, BCh, FFARCS*

St Thomas's Hospital

J. M. HALL, MB, BS, FFARCS*

Guy's Hospital

A. BRACKEN, PhD, FRIC

G. GOULDSTONE

D. S. NEWLAND, BSc

British Oxygen Research & Development Ltd

The possibility of solving the problem of anæsthetic explosions by the introduction of a new non-inflammable inhalational anæsthetic has received considerable attention since the Second World War. Stacey[1] refers to the chemical inertness and non-inflammability of fluorine analogues of organic compounds. It, therefore, appears reasonable to investigate fluorine compounds as possible non-inflammable anæsthetics which are stable to soda lime. Raventós[2] has reviewed the literature concerned with work on fluoro-derivatives of hydrocarbons. Following work on xenon[3], several fluoro-hydrocarbons have been tested for anæsthetic properties on mice. A small number of compounds were obtained privately; and a second, larger number have been made at Birmingham, in Professor Stacey's department, on behalf of the Medical Research Council's Committee on Non-explosive Anæsthetic Agents.

* In receipt of a Medical Research Council grant
This work was carried out in the Inter-departmental Laboratory at Guy's Hospital

The first group of compounds to be tested is shown in TABLE 1.

Table 1

First group of compounds

HALOGENATED HYDROCARBON	CHEMICAL FORMULA	BOILING POINT °C	QUANTITIES
1,1,2,2-tetrafluoroethyl ethyl ether	$C_2HF_4.O.C_2H_5$	58°	Not restricted
1,1,1-trifluoro-2-propanol	$CF_3.CH(OH)CH_3$	77°	20g
1,1,1-trifluoro-2-methyl-2-propanol	$CF_3C(CH_3)OH.CH_3$	80° (m.p. +18°C)	20g

Very simple tests for anæsthesia were carried out on these drugs, and in view of their inflammability more detailed tests were not undertaken.

Tests for anæsthesia consisted of placing a plug of cotton wool with a few drops of the compound on it in a 6in × ½in test tube. The plug was placed about ¾in from the top of the tube and the mouse was held with its face in the mouth of the tube. The degree of anæsthesia was assessed in the following ways:

Cessation of struggling
Lack of response to painful stimuli
Presence or absence of corneal reflex.

Physical and chemical tests were limited to a simple test of inflammability, and tests of purity in all three cases and an examination of the stability to soda lime of the propanol derivatives.

The inflammability test was carried out by applying a small flame to about 0.5ml of the liquid exposed on a small watch glass.

The test of stability to soda lime was done in conjunction with gas chromatography as a test of purity. This test was used in both groups of compounds and is described in the accompanying paper.

The results with this first group were as follows:

(a) *Tetrafluoroethyl ethyl ether*

(1) Inflammability. Burned in air. (2) Purity. There was one impurity (less than 0.5 per cent) in the sample. (3) Anæsthetic properties. One mouse was anæsthetised as satisfactorily as would have been expected with diethyl ether. There was no coughing on induction and recovery was rapid and uneventful. A second mouse was anæsthetised on four separate occasions, being allowed to recover fully in between each test. After three hours both mice appeared to be fit. (4) Discussion. This compound appears to be a satisfactory anæsthetic. Induction of anæsthesia was rapid, with no struggling. The inflammability of this compound was a disappointment. Hanford and Rigby[4] state that the substance is non-inflammable. It was thought originally that an

impurity might have been the cause of the inflammability, but a purified sample was also found to be inflammable.

(b) *Trifluoro-propanol*

(1) Inflammability. Burned in air with a smoky flame. (2) Purity. One impurity was shown to be present. (3) Stability to soda lime. This substance and its impurity did not react with soda lime. (4) Anæsthetic properties. One mouse breathed the vapour for several minutes without any apparent effect. A second mouse behaved similarly at first, but very suddenly stopped breathing and was found to be dead. A third mouse became unconscious after seven minutes, but did not appear to be fully recovered after a further twenty minutes. (5) Discussion. The fact that this substance is inflammable is not recorded in the literature. It was not a promising anæsthetic and in view of its inflammability no further work has been done on the drug.

(c) *Trifluoro-methyl-propanol*

(1) Inflammability. Burned in air with a smoky flame. (2) Purity. Three impurities were shown to be present. (3) Stability to soda lime. No reaction by the compound or the impurities. (4) Anæsthetic properties. One mouse appeared to be unaffected by the vapour after several minutes, but then died suddenly. A second mouse was anæsthetised to the stage of an absent corneal reflex but took some forty minutes to recover. (5) Discussion. This substance was not pure and burned in air. Its anæsthetic properties were not encouraging and no further work has been done on it.

THE SECOND GROUP OF COMPOUNDS

Most of the compounds in this group were made in Birmingham University but two were obtained privately.

Details are given in TABLE 2.

There does not appear to be any record in the literature of any pharmacological examination of 1,2-difluoro-1-chloroethylene, 1H-pentafluorocyclobut-1-ene, or 1H,2H-hexafluorocyclobutane. 1,2-Dichlorohexafluorocyclobutane is reported to be toxic[5]. Several references have been found to hexafluorocyclobutene. Its melting point has been quoted as −60°C[6], −59°C[7] and −61°C[17], while its boiling point has been stated to be 1°C[6] and 5°C[7]. It is also said to be non-toxic[8].

Henne[9] quotes the boiling point of trifluoroethylene as −51°C while it is quoted in the suppliers' catalogue* as −53°C. No reference has been found to any physiological activity of this substance.

*Columbia Chemicals Co's Catalogue 7. June 1954

Table 2

Second group of compounds

CPD. NO.	HALOGENATED HYDROCARBON	CHEMICAL FORMULA	BOILING POINT °C	QUANTITIES 1 grams	2
Compounds from Birmingham University					
1	1,2-difluoro-1-chloro-ethylene	HFC=CFCl	−5	5	2.2
2	Hexafluorocyclobutene	F_2C-CF $\vert \quad \Vert$ F_2C-CF	3	4	3.7
3	1,2-dichlorohexafluoro-cyclobutane	$F_2C-CFCl$ $\vert \quad \vert$ $F_2C-CFCl$	59	3.2	4.1
4	1H-pentafluorocyclobut-1-ene	F_2C-CF $\vert \quad \Vert$ F_2C-CH	25	3.3	1.2
5	1H,2H-hexafluorocyclo-butane	F_2C-CHF $\vert \quad \vert$ F_2C-CHF	26	3.2	7.3
6	1H/2H,4H-nonafluoro-cyclohexane		101	Not restricted	
7	1,2-difluoro-1,2-dichloroethylene	CFCl=CFCl	21	25	0.4
8	1,1,2-trifluoro-1,2-dichloroethane	$CF_2Cl.CHFCl$	30	9	0.9
9	1,1,2-trifluoro-1,2,2-trichloroethane	$CF_2Cl.CFCl_2$	47	33	—
10	1,2-difluorotetrachloro-ethane	$CFCl_2.CFCl_2$	91 (m.p. 25)	20	—
Compounds obtained privately					
11	Trifluoroethylene	$CF_2=CHF$	−53	100	—
12	2-trifluoromethyl-1-propene	$CH_3.C(CF_3)=CH_2$	6	100	—

2-trifluoromethylpropene boils at 6°C[9]: Go Lu[10] states that a concentration of 75 per cent produces an anæsthetic effect in dogs.

No references have been found to the inflammability, stability to soda lime, or toxicity of the remaining compounds in TABLE 2.

Experimental technique

The experiments in the first group of compounds had emphasised: (1) The need for purity of the sample; (2) The need for being able to administer known concentrations of pure drugs to mice even when the quantity available was very small.

For the second group of compounds, apparatus was designed which enabled more accurate tests to be carried out.

This apparatus is shown diagrammatically in FIG. 1 and photographically in FIG. 2. If the drug was a gas at room temperature a reservoir system (FIG. 3) was used to introduce the sample. If the drug was a liquid at room temperature a simplified apparatus (FIG. 4) was used. Oxygen was blown over the surface of the liquid at a constant rate. When necessary the liquid was surrounded by melting ice or warm water to maintain an even temperature. It will be seen from column five of TABLE 2 that the quantities were limited and were sometimes obtained as two separate samples.

The gas reservoir (FIG. 3) consisted of a glass vessel containing mercury, the level of which could be adjusted by raising or lowering a second glass vessel. In the diagram the stationary vessel is on the left and is connected to the moving vessel by a rubber tube. It was necessary to raise the moving vessel by a screw thread device mounted on a Dexion framework because of the mass of mercury involved. Mercury and glass sinter non-return valves were used to prevent loss of gas from the reservoir by solution in the tap-grease. These valves function because the glass sinter is too fine for mercury to pass through but allows the passage of gas. The holder can take up to 1 litre of gas sample.

When it was required to empty an ampoule into the gas holder the stationary vessel was filled with mercury by raising the movable one. The ampoule was cooled in liquid oxygen to solidify the contents and reduce the pressure and the neck of the ampoule was broken off. The ampoule, still maintained in liquid oxygen, was connected to the gas inlet by rubber tubing which was then evacuated together with the space between the tap on the gas inlet and the glass sinter. The ampoule was removed from the liquid oxygen, and the compound allowed to melt and then boil, the gas passing into the gas holder, where the pressure was maintained at atmospheric by adjustment of the mercury levels.

The mouse test apparatus was arranged to be as simple as possible, consistent with giving the test animal a known concentration of compound. To guard against any accumulation of carbon dioxide in the circuit, a small soda lime guard tube was fitted between the rubber reservoir bag (shown on the extreme right in FIGS. 1 and 2) and the mouse container. In some of the earlier experiments this was not used and the length of time for which the mouse could be left in the container was thereby restricted. Gas analysis of the final mixture was carried out on each occasion. The methods used are described in the accompanying paper.

The estimated volume of oxygen required was taken into the gas burette by disconnecting the mouse container at 'A' and by suitable adjustment of the double-oblique tap 'B'. The gas burette was then

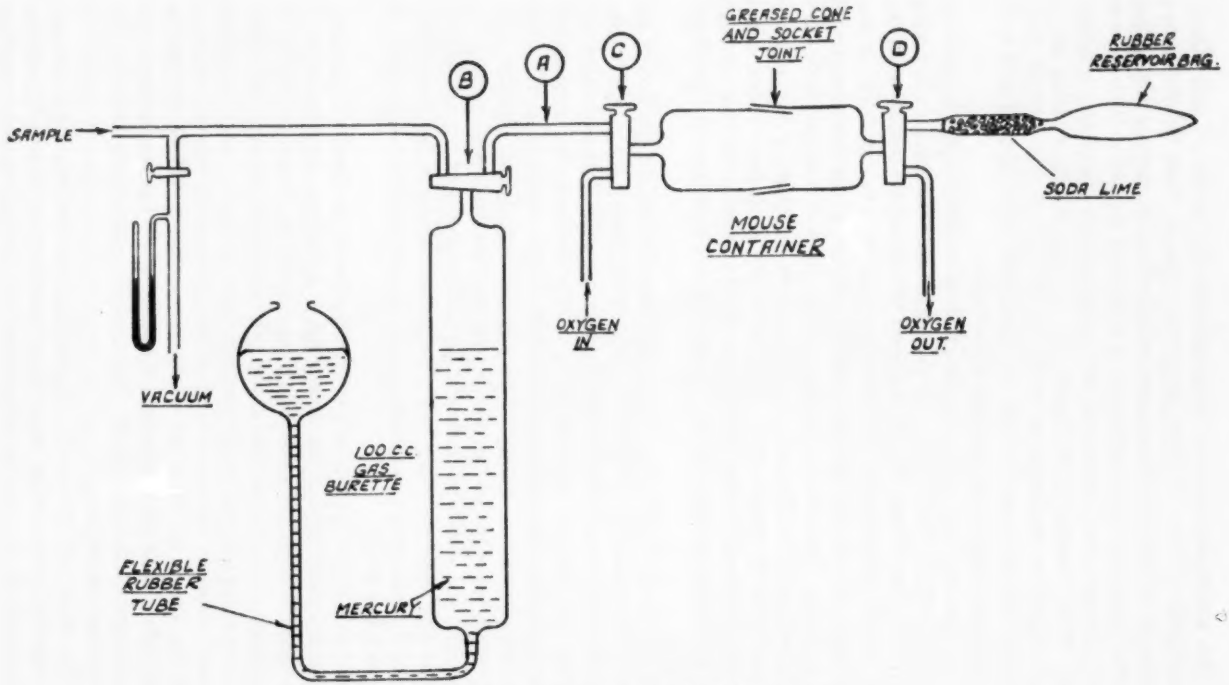


FIG. 1 Mouse test apparatus circuit diagram

filled to 100ml with the test compound from the gas holder after the connecting tube had been evacuated to remove the air. The method of estimation was based on the volume of the apparatus. The volume of the mouse container was 67ml, and that of the connecting tubes and the inter-granular air space in the soda lime was 5ml. The volume of a dead mouse, similar to those used in the experiments, was found to be 16ml. This meant that the total gas space in the system, including the burette, was $100+67+5-16=156$ml. If, for example, it was desired to give 20 per cent of a compound in oxygen, it was necessary to pass 31.2ml into the burette with 68.8ml of oxygen. The rest of the oxygen was in the mouse container and tubes.

The mice used were white albinos about three weeks old. One mouse was used per test and after marking, was placed in the container which was then reconnected and the double-oblique taps 'C' and 'D' set so that oxygen could flow through the mouse chamber. The rubber reservoir bag was completely emptied before tap 'D' was set to allow oxygen to escape. The oxygen flow was started (flow-rate 300ml per minute). Oxygenation was carried out for ten minutes in order to eliminate all significant amounts of nitrogen from the circuit. When this had been completed, the oxygen flow was stopped, and taps 'B', 'C' and 'D' were adjusted to connect the mouse container to the gas burette and the rubber reservoir bag through the soda lime. The mercury level in the burette was alternately raised, to pass the gas mixture through the mouse container, and soda lime into the reservoir bag, and lowered to return it to the burette. This was done in order to mix the gases contained in the burette with those in the mouse container, and ensured that approximately two-thirds of the gas mixture actually passed through the soda lime at each manipulation. The raising and lowering was carried out in such a way that the gas flow through the apparatus was about 100ml per minute. Each experiment was terminated at a point when the gas burette was full of gas mixture, so that a sample could be obtained for analysis in the evacuated tube shown at the extreme left in FIG. 2. This tube contained a small quantity of mercury and was stored inverted in transport, so that the mercury maintained a barrier between the sample and the tap grease.

Where the compound to be tested was a liquid (or, in one case, a solid), the apparatus was slightly modified as shown in FIG. 4. A simple vaporiser and a constant gas flow technique were used. The vaporiser consisted of a test tube having a ground glass socket fitted with a wash bottle type head. Variations of the level of the liquid in the tube, the gas flow rate, and the temperature of the bath surrounding the vaporiser, were used to obtain various concentrations of the compound in oxygen. The sample tubes were placed in position at

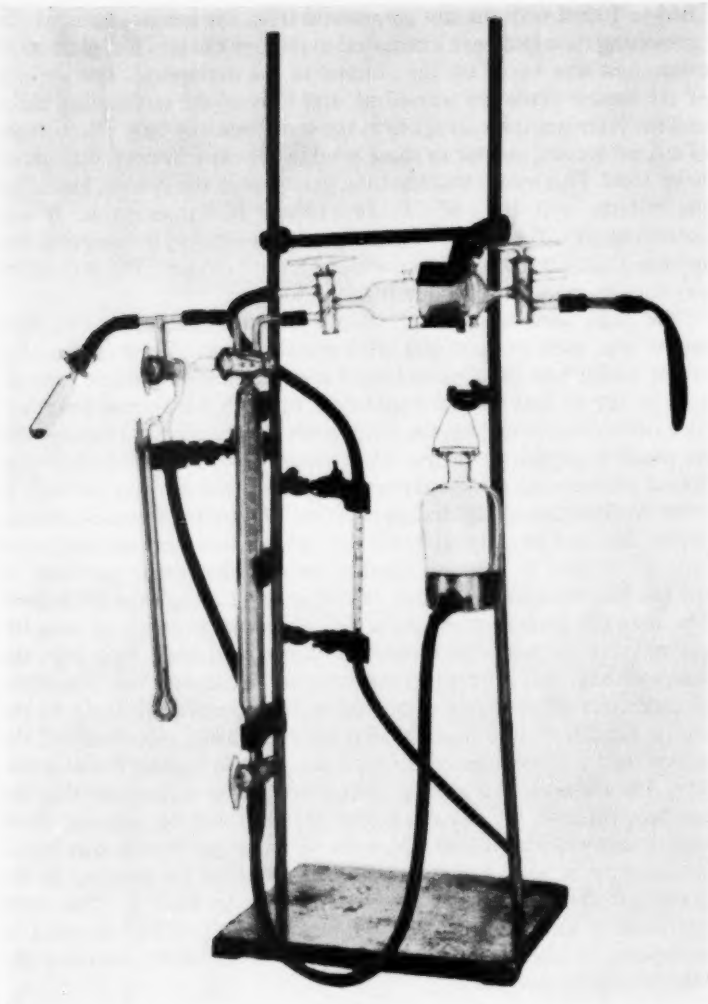


FIG. 2

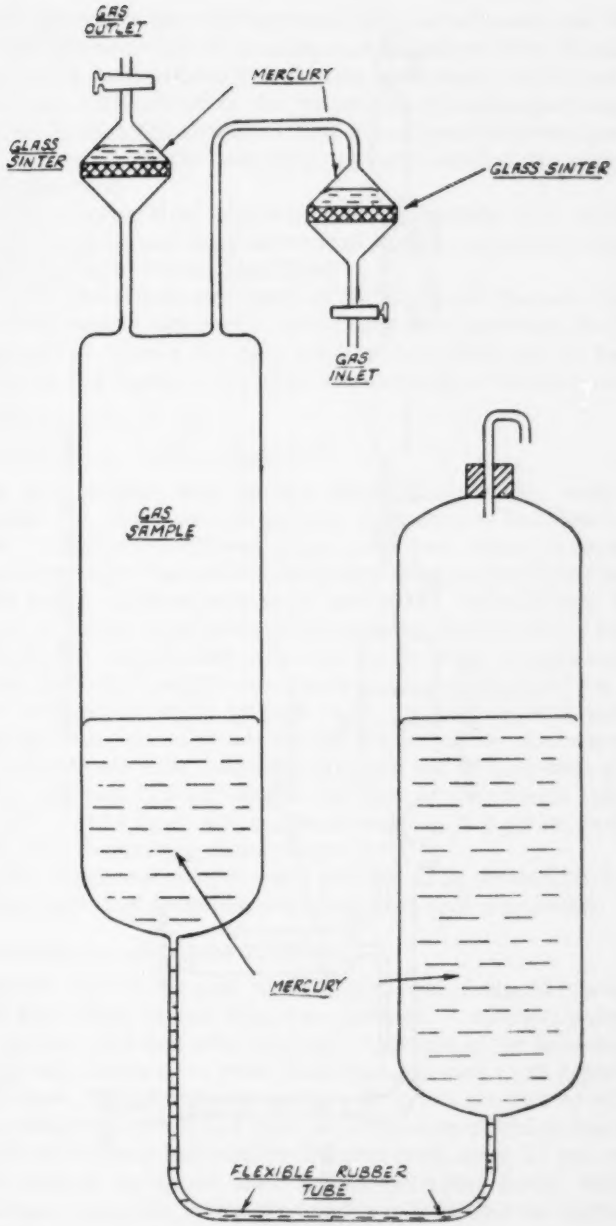


FIG. 3 Gas reservoir

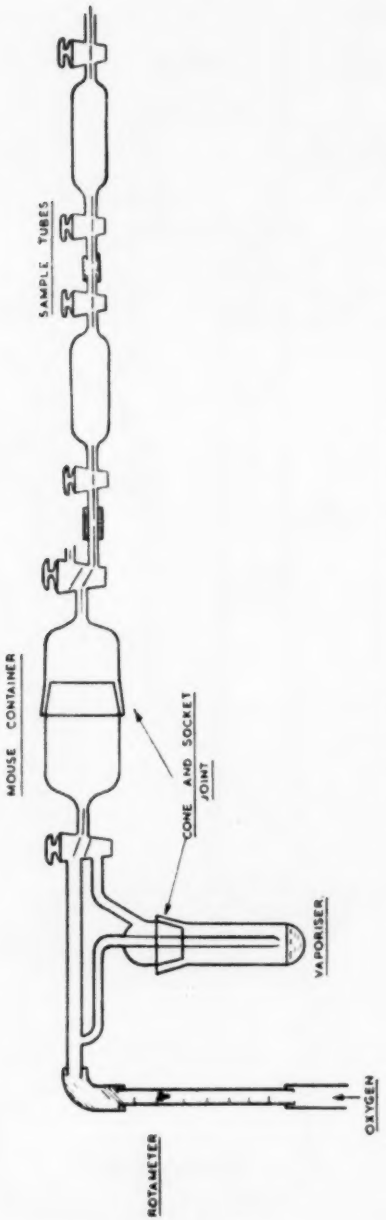


FIG. 4 Open circuit mouse test apparatus

the beginning of the experiment and were not removed until the end.

The inflammability of the compounds obtained from Birmingham University was examined by collecting (over water) the mixture, which had been administered to the test mouse, in a 20ml glass-stoppered bottle. Ignition was attempted using a small semi-luminous gas flame. Limitation of supplies prevented any more detailed investigation of inflammability.

The inflammability limits of trifluoroethylene and 2-trifluoromethylpropene have been determined using an apparatus which was basically that of Coward and Jones[11].

Tests of anæsthesia were based on (1) Movement (purposive or not); (2) Respiration (voluntary – *e.g.* 'sniffing', or automatic); (3) Lack of response to tapping the glass container; (4) Response to touching whiskers and degree of flaccidity, on removal from the container.

Experimental results

1,2-Difluoro-1-chloroethylene[12]

The first samples were impure, having three major components (50 per cent, 38 per cent, 10 per cent; there were cis and trans isomers and 1,1-difluoro-2-chloroethylene) and two minor components. Also some slight reaction with soda lime was apparent. Tested without soda lime it produced uneventful anæsthesia, but with soda lime in circuit it produced convulsions in concentrations as low as 8 per cent.

A further sample had only two components, in approximately equal proportion, which were the cis and trans isomers of this olefin. The sample was stable to soda lime; experiments both with and without soda lime in circuit showed similar results. Anæsthesia was produced in all cases; induction was rapid and in most cases smooth. Mice receiving 12.9 per cent to 16.7 per cent recovered (with one exception at 14.7 per cent) and mice receiving 21.8 per cent and over died without regaining consciousness.

This compound showed some promise as an anæsthetic, but it is inflammable and, therefore, no further work on it is proposed.

Hexafluorocyclobutene[7]

Between 5 and 6 per cent of the first sample produced convulsions and then death in less than four minutes. A mouse survived for one-and-a-half hours after inhaling 2.7 per cent of the second sample which was shown to be pure. Soda lime was used in all experiments with both first and second samples. It is not possible to rule out completely the presence of toxic decomposition products, but all the available evidence incriminates the drug itself, since 2.7 per cent for four minutes produced death in one-and-a-half hours. Owing to shortage of supplies, no test for stability to soda lime was carried out.

One test of combustion was carried out on a sample in which the concentration was 19 per cent in oxygen. Non-explosive combustion took place. It is felt that the presence of an ethylenic double bond is responsible for this inflammability of a fully fluorinated hydrocarbon. In view of its inflammability as well as its effects on the mice, no further investigations are proposed on this drug.

1,2-Dichlorohexafluorocyclobutane[7]

As this compound boils at 59°C it was initially tested on a plug of cotton wool in a test tube. The mouse's nose was pushed into the test tube, but did not actually touch the cotton wool. The mouse died, following convulsions, in one minute forty seconds.

Three concentrations were tried in the mouse test apparatus (FIG. 2); 6 per cent did not produce any effect; 13.6 per cent produced convulsions; 20.9 per cent killed the mouse in thirty seconds. There were severe lesions in the lungs and the heart was also affected. Soda lime was used in these three experiments.

None of these last three mixtures proved to be inflammable, but in view of its toxicity it is felt that the drug should not be further investigated.

1,H-Pentafluorocyclobut-1-ene[13]

The first sample had three major components (8 per cent, 25 per cent, 65 per cent) and two minor components. One of the major components was removed on contact with hot soda lime. Soda lime was used in three experiments, all of which resulted in convulsions and death.

A further sample had two major components only (79 per cent and 21 per cent). The impurity is now known to be an isomeric olefin[14]. It reacted seriously with soda lime and again produced convulsions and death in all experiments, even two in which no soda lime was used. Although the purity of the sample tested was unsatisfactory, it does not seem likely that further investigation of this compound is called for since in all probability the pure compound will be inflammable, toxic, and react with soda lime.

1H,2H-Hexafluorocyclobutane[13]

The first sample showed definite anæsthetic properties. It was contained in two tubes, the contents of which gave rather different results, one producing three deaths in five experiments. All tests were done with soda lime in circuit. Unfortunately no purity or soda lime tests were carried out.

A further sample was pure but no soda lime test was carried out. Two experiments with this sample gave very deep anæsthesia, in concentrations of 10.5 per cent and 11.4 per cent, with rapid recovery.

The constant gas flow technique was used and so no soda lime was necessary.

This compound was not without interest as an anæsthetic, but its lower inflammability limit in oxygen was shown to be approximately 7 per cent and so no further work is proposed on the drug.

1H/2H,4H-Nonafluorocyclohexane[15]

Concentrations of 2.9 per cent, 2.1 per cent and 1.7 per cent killed mice after exposures of less than ten minutes following violent convulsions and opisthotonus. Further tests did not appear to be indicated.

1,2-Difluoro-1,2-dichloroethylene[12]

This drug produced anæsthesia in concentrations of 11 per cent, 15 per cent and 25 per cent. Induction was smooth and recovery always appeared complete in two to three minutes. It did not appear to react with soda lime, but the compound burned in oxygen.

1,1,2-Trifluoro-1,2-dichloroethane (containing 10 per cent 1,1, 2-Trifluoro-2,2-dichloroethane)[12]

This compound was a mixture, but as it was not separable by distillation it has been regarded as a pure substance for our purpose. In view of the low boiling point of the compound it was surrounded by a cold bath. Using this technique, 15 per cent of the compound was obtained and this caused the mouse to die after two minutes' exposure, but without any signs of distress. A second mouse was anæsthetised with 8 per cent of the drug. Exposure was for one minute. The mouse was removed at this time as anæsthesia seemed profound, but recovery appeared complete in about one minute. A third mouse was exposed to 8 per cent for a minute-and-a-half. Anæsthesia was produced in thirty seconds. Induction was smooth and rapid and recovery appeared complete in one-and-a-half minutes.

The drug is non-inflammable in oxygen and does not react with soda lime.

1,1,2-Trifluoro-1,2,2-trichloroethane[12]

Six per cent of this compound anæsthetised a mouse in two minutes. Recovery was rapid. Twenty-five per cent of the compound killed a mouse in ninety seconds. At the saturation vapour pressure at room temperature, the substance was non-inflammable in oxygen. There was no reaction with soda lime.

1,2-Difluorotetrachloroethane[12]

An interesting point about this substance is that it is a solid at room temperature, having a melting point of 25°C. With 1.7 per cent a

mouse was anæsthetised and recovery was rapid. 1.8 per cent of the compound produced anæsthesia. Recovery was rather slow, but appeared complete after some ten minutes. 2.1 per cent produced very deep anæsthesia down to respiratory arrest. Recovery was slow but complete. Induction was not smooth at any of these concentrations.

The substance could not be made to burn in air or oxygen.

There was no significant reaction with soda lime.

Trifluoroethylene

No anæsthetic effects were observed with this compound, even when a concentration of 76.9 per cent in oxygen was used. Soda lime was not used in the experiments and the sample was shown to be pure. The inflammability limits have been determined in air as 17.4 per cent (lower limit) to between 25 per cent and 30 per cent (upper limit).

2-Trifluoromethyl-1-propene

This compound was tested with and without soda lime. The compound itself was not affected by heating with soda lime, but two slight impurities were removed. It had some anæsthetic effect in concentrations of 25 per cent to 50 per cent. In view of the fact that its inflammability limits in air are from 4 per cent to 11 per cent, no further work is proposed on this drug.

Compounds 8, 9 and 10 in TABLE 2 appeared to possess, in some measure, the properties in which we were interested. They produced anæsthesia, they were non-inflammable and they did not react with soda lime. Accordingly, larger supplies were obtained, and these were sent to Professor J. H. Burn, the Chairman of the Non-explosive Anæsthetics Committee of the Medical Research Council, who has now published the results of a more detailed investigation of their anæsthetic properties[16].

DISCUSSION

The compounds tested were selected on the basis of being either readily available, or of being closely related chemically to known anæsthetics. For example, trifluoroethylene may be regarded as 'trilene' with all the chlorine atoms replaced by fluorine. It is of interest that this compound proved to be more inflammable than 'trilene', but to be devoid of anæsthetic properties.

One feature of the work reported here, was that it was considered to be undesirable to go to the expense of preparing large quantities of substances which might prove to be useless as anæsthetics. Therefore, in most cases, only small quantities were used, and much thought was given to the problem of how to administer these in known concentrations; in fact this problem was largely solved, but it would be better

to be able to use larger quantities of material because of the more reliable results which could be expected if more mice were used per experiment. Similarly, the small quantities available severely limited the amount of testing for inflammability which could be carried out. Within these limits it is felt that the results obtained justify certain conclusions.

The first is that when simple fluorine compounds contain double bonds, they are more chemically reactive as shown by the inflammability, than might have been supposed from the well-known chemical inertness of highly fluorinated compounds. For example, one would not have expected, from its chemical formula C_4F_6, that hexafluorocyclobutene would have been inflammable.

The second conclusion is, that in the range of volatile fluorine compounds, there is a large number of anæsthetics of varying potency, but, unfortunately, also of varying toxicity. One drug, nonafluorocyclohexane, produced convulsions and death without any appearance of anæsthesia. Of the other fourteen compounds tested, seven showed definite anæsthetic properties, and three of these were of such promise that larger-scale experiments were undertaken, as reported by Burn[16]. This can be regarded as a high proportion in view of the almost random selection of the drugs for testing.

A reference should be made to one of the compounds, namely difluorotetrachloroethane, which was solid at room temperature, with a vapour pressure high enough to give a concentration in oxygen around 2 per cent.

In one experiment an effort was made to administer a higher concentration by surrounding the solid with a bath of hot water. This raised the temperature of the solid above its melting point of 25°C, but as soon as the oxygen flow impinged on the surface of the molten solid this caused crystallisation at that point. This was accompanied by local cooling due to the latent heat of crystallisation, so that the concentration of substance in the vapour phase was not increased. This would appear to be a type of anæsthetic with which it is almost impossible to give an overdosage. It is unfortunate that in this particular case, Burn was able to show that it had undesirable side-effects.

One aspect of the work which will be of interest to an anæsthetist, is that many of the substances, in addition to being closely related to 'trilene', were in fact made from 'trilene' as the starting material[12]. This also meant that most of these compounds contained chlorine as well as fluorine, so that it is not clear from our results whether the undesirable effects are in fact due to the presence of fluorine atoms or chlorine atoms. The toxic substances which contained fluorine alone were compounds containing a double bond, or ring structures, or

both. Therefore, no firm conclusions can be drawn as to the degree of toxicity to be expected from a highly fluorinated compound, free from chlorine and not possessing a double bond or ring structure.

The present evidence agrees with the widely accepted view that such compounds are not rendered physiologically dangerous merely by the presence of fluorine atoms. It confirms the interest now felt, in pursuing the use of fluorine compounds as possible agents for non-explosive anæsthesia and the work, therefore, continues.

References

[1]STACEY, M. (1948). Royal Institute of Chemistry Lecture 'The new Fluorocarbon Chemistry'.
[2]RAVENTÓS, J. (1956). *Brit. J. Pharmacol.*, *2*, 394.
[3]BRACKEN, A., BURNS, T. H. S. and NEWLAND, D. S. (1956). *Anæsthesia*, *11*, 40.
[4]HANFORD, W. E. and RIGBY, G. W. (1947). U.S.P., 2,409,274.
[5]SPIEGL, C. J. (1953). *Natl. Nuclear Energy Ser: Div. VI*, Vol. I, Book 3, 2291.
[6]GROSSE, A. V. and CADY, G. M. (1947). *Ind. Eng. Chem.*, *39*, 367.
[7]BUXTON, M. W., INGRAM, D. W., SMITH, F., STACEY, M. and TATLOW, J. C. (1952). J.C.S., 3830.
[8]PARK, J. D., BENNING, A. F., DOWNING, F. B., LAUCIUS, J. F. and MCHARNESS, R. C. (1947). *Ind. Eng. Chem.*, *39*, 354.
[9]HENNE, A. L. (1944). *Organic Reactions* (Wiley, U.S.A.), *2*, 49.
[10]LU, G., JOHNSON, S. L., LING, M. S. and KRANTZ, J. C. (1953). *Anesthesiology*, *14*, 466.
[11]COWARD, H. F. and JONES, G. W. (1952). Bulletin 503. Bureau of Mines (U.S. Government Printing Office), Washington.
[12]FULLER, G., STACEY, M., TATLOW, J. C. and THOMAS, C. R. (1960) *Tetrahedron* (in the press).
[13]BUXTON, M. W. and TATLOW, J. C. (1954). *J. chem. Soc.*, 1177.
[14]FULLER, G. and TATLOW, J. C. (1960). Personal communication.
[15]GODRELL, J. A., STACEY, M. and TATLOW, J. C. (1958). *Tetrahedron*, *2*, 193.
[16]BURN, J. H., EPSTEIN, H. G. and GOODFORD, P. J. (1959). *Brit. J. Anæsth.*, *31*, 518.
[17]SLESSOR, C. (Editor) (1951). 'Preparation, properties and technology of fluorine and organic fluoro-compounds. McGraw Hill, U.S.A.

An investigation of new fluorine compounds in anæsthesia (2)

Analysis by gas chromatography

J. H. GLOVER, BSc, FRIC

H. W. HODGSON, ARIC

British Oxygen Research & Development Ltd

In the search for a non-inflammable anæsthetic many very similar compounds have been examined. The particular group under consideration contains the fluoro-substituted paraffins and olefines, which may also be partially substituted with other halogens.

It is essential to have information on the purity of the materials under test, and owing to the similarity of the compounds examined, only methods of analysis based on physical properties could be of use. The technique of gas chromatography is of particular application in this case, and was used successfully in the analysis of these compounds.

Gas chromatography is a technique originally developed by James and Martin[1] for the separation of a mixture of fatty acids and has since been applied to many analytical problems. The principle of the method is the partition of the sample, in the gas phase between a mobile gaseous phase and a stationary liquid phase. Differences in the solubility of the components of a mixture result in differences in the time that components are retained by the liquid phase, and it is these differences that form the basis of the separations achieved.

In practice, the stationary phase consists of a high-boiling, heat-stable liquid, which is dispersed on an inert powder of high surface area; celite, or kieselguhr is much used for this purpose. The dispersed stationary phase is packed into a long column, usually a tube of 2–4mm bore and of a length adequate for the particular separations to be carried out: a six foot column is enough for most purposes although much longer columns can be used. The mobile phase is an

inert gas, usually nitrogen or hydrogen, which passes through the column at a constant rate.

A small quantity of the mixture to be separated is injected into the mobile phase at the entrance to the column, separation occurs as the components pass along the column at different rates and the separate components may be detected in the gas stream emerging from the column.

It can be shown that the efficiency of separation is inversely proportional to the amount of sample to be separated, so that as small a sample as possible is used. This consideration means that the method of detecting the emergent fractions must be very sensitive, detection must also be of a non-specific nature since many varied fractions will be encountered.

The most widely used method of detection is the measurement of the thermal conductivity of the effluent carrier gas; this property is

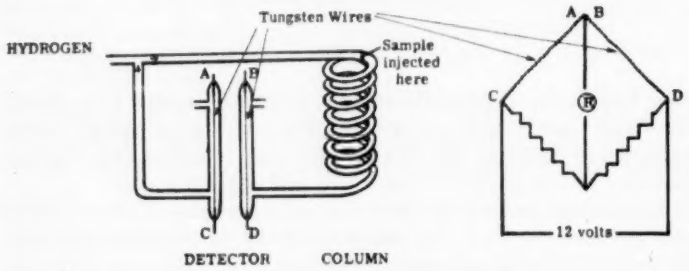


FIG. 1 Gas chromatography apparatus

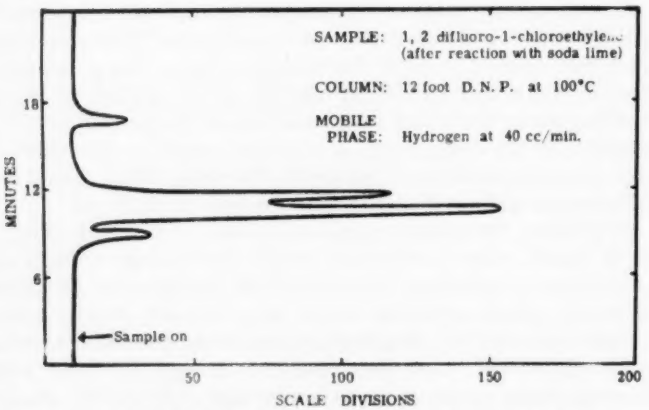


FIG. 2 Section of recorder chart showing a typical chromatogram

usually compared continuously with the thermal conductivity of the pure carrier gas.

The detector consists of two glass tubes each containing a fine tungsten wire along its longitudinal axis. The wires are identical in every respect and are made to form two arms of a Wheatstone bridge. They are heated by the current in the bridge, and the effluent carrier gas from the column is passed through one tube, and the pure carrier gas through the other. Any change in the thermal conductivity of the effluent gas causes a change in the temperature of the wire and thus its resistance and results in an electrical output from the bridge.

It is convenient to record the output continuously on a strip-chart pen recorder, the emergence of a fraction from the column is then indicated by a peak on the chart. Under fixed conditions, the position of the peak on the time scale is characteristic of a particular compound and the area beneath the peak is proportional to the quantity of material in the fraction. The apparatus is shown in FIG. 1, and a typical chromatogram in FIG. 2.

APPLICATION OF GAS CHROMATOGRAPHY

Information was required on two points, first on the purity of the materials to be evaluated as anæsthetics and second on their behaviour with soda lime. The necessity for pure materials is obvious, and it is also essential that compounds should not form toxic materials on reaction with soda lime.

PURITY TESTS

These were carried out by introducing a sample of the test material into the chromatographic column and observing the number and relative heights of peaks obtained.

Conditions were as follows:

Column length	12ft
Stationary phase	Dinonyl phthalate on kieselguhr
Mobile phase	Hydrogen
Column temperature	20°C for gases, 100°C for liquids
Flow rate	40ml/min

No attempt at quantitative analysis was made since pure specimens of the various impurities were not available for calibration purposes. The peak heights were used to indicate whether impurities were major or minor constituents.

REACTION WITH SODA LIME

An empirical test was devised to determine the extent of reaction with soda lime. A tube was made from thick-walled pyrex tubing of about

Table 1

Examination of halogenated hydrocarbons using gas chromatography

HALOGENATED HYDROCARBONS		RELATIVE PEAK HEIGHTS																
RETENTION TIME (MIN)		2½	3½	4	7	7½	8½	9	9½	10½	13½	14	15	15½	17	19	23	25	28
1:2-difluoro-1-chloroethylene	Batch C12	6	—	1	140	—	685	—	520	—	—	—	—	—	—	—	1	—	—
Hexafluorocyclobutene	Batch E8	—	300	—	—	—	—	1	—	4	—	—	—	—	—	—	—	—	—
1:H-pentafluorocyclobut-1-ene	Batch F5	158	—	—	—	—	—	—	—	—	—	50	—	400	—	—	—	3	6
2-trifluoromethylpropene		—	—	—	—	1	—	—	—	—	480	—	—	—	10	16	—	—	—
Trifluoroethylene		—	—	500	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Table 2

Examination of halogenated hydrocarbons using gas chromatography, after treating with soda lime

HALOGENATED HYDROCARBONS		RELATIVE PEAK HEIGHTS																
RETENTION TIME (MIN)		2½	3½	4	7	7½	8½	9	9½	10½	13½	14	15	15½	17	19	23	25	28
1:2-difluoro-1-chloroethylene	Batch C13	—	—	—	26	—	144	—	110	—	—	—	20	—	—	—	—	—	—
1:H-pentafluorocyclobut-1-ene	Batch F5	—	—	—	—	—	—	—	—	—	—	50	—	400	—	—	—	3	6
2-trifluoromethylpropene		—	—	—	—	—	—	—	—	—	200	—	—	—	—	—	—	—	—

1cm internal diameter, 1–2g of soda lime was introduced, followed by a sample of the material under test, which in the case of a gas was condensed into the tube by cooling to −78°C. Enough sample to cover the soda lime was taken and the tube and contents cooled to −78°C with acetone and solid carbon-dioxide before sealing. The final cooling was introduced to make sure that there was no de-composition by heat of the sample during the sealing operation.

The sealed tubes were then maintained at 70°C for three hours, cooled, opened and the sample re-examined by gas chromatography. Any difference in the number of fractions obtained, or the relative amounts of different fractions was taken as evidence of reaction with soda lime. The soda lime was not examined, since the object of the test was to investigate the formation of volatile products only.

RESULTS

The results obtained on five typical compounds are shown in TABLE 1. Only trifluoroethylene is completely free from impurities, although hexafluorocyclobutene and 2-trifluoromethylpropene only contain minor amounts.

TABLE 2 shows the analysis by gas chromatography of three materials after treatment with hot soda lime. A new fraction is observed at fifteen minutes in the case of 1,2-difluoro-1-chloro-ethylene and the large fraction at two-and-a-half minutes is removed in the case of 1,H-pentafluorocyclobut-1-ene: 2-trifluoromethylpropene is unaffected except for the removal of the minor constituents.

The authors thank the Directors of British Oxygen Research & Development Co Ltd, for permission to publish this article.

Reference

[1] JAMES, A. T. and MARTIN, A. J. P. (1952). *Biochem. J.*, *50*, 679.

Serum glutamic oxalacetic transaminase activity following hypothermia

OTTO W. WENDEL, DSc

Department of Chemistry
Bethany College, Bethany, W. Va.*

The increased use of hypothermia during extensive cardiovascular surgery has created a series of new problems for the surgeon and a new area for investigation by the physiologist. General acceptance of hypothermia as a standard procedure has been deterred because of the frequency of ventricular fibrillation[1 2] and possible pathologic[3 4 5] and metabolic alterations[6 7 8] which are either difficult to control or are irreversible. Although numerous investigations of physiologic processes during the hypothermic state have been conducted, little information has been obtained which might be employed diagnostically.

Wroblewski[9] has reviewed the clinical significance of serum transaminase activities. However, no reference was made to changes in transaminase activity following hypothermia. The measurement of plasma glutamic oxalacetic transaminase activity has been applied in this laboratory for the detection of possible cellular damage incurred during chlorpromazine-induced poikilothermia[10]. It is well established that serum glutamic oxalacetic transaminase (SGOT) increases markedly following injury of various tissues. The original observation by La Due *et al*[11] of the elevation in transaminase activity in cases of acute myocardial infarction in humans, has been confirmed by Steinberg and Ostrow[12] and supported by studies of experimentally produced myocardial infarcts in dogs[13 14 15]. In both clinical and experimental cases the SGOT increases within one or two days to peak values two to twenty times the normal range and returns to normal within three to six days. Rudolph *et al*[15] have shown the same changes following experimental infarct in lung, kidney, spleen and bowels of dogs. Marked increases in SGOT are reported to occur in acute

* now at Sterling-Winthrop Research Institute, Rensselaer, New York

hepatitis and carbon tetrachloride poisoning[16] and following skeletal muscle trauma[14], however, Nickell and Allbritten[17] report only slight increases following abdominal surgery.

Elevations in SGOT apparently result from the release of transaminase enzyme from damaged cells into the systemic blood. Evidence in support of this concept was presented by Nydick *et al*[14], who found the glutamic oxalacetic transaminase content of infarcted myocardium exhibiting recognizable tissue necrosis to be 2 per cent of that in normal myocardium. Wroblewski and La Due[16] found that for a variety of diseases the SGOT remains normal unless tissue destruction occurs. No elevation in SGOT was found following ischemia of the heart and other organs[12 15]. One must not, however, altogether exclude the possibility that there may exist physiological conditions in which cellular injury is short of necrosis and still SGOT activity increases. For instance, if the mechanism for the removal of transaminase should become impaired, the SGOT would increase.

In the present study the first situation examined was surface immersion hypothermia, as employed surgically. The study was then extended to investigate the factors of ventilation and duration of hypothermia. This report describes changes in SGOT activity in dogs following six experimental conditions.

MATERIALS AND METHODS

Forty-eight mongrel dogs of both sexes weighing 12–15 kilograms were divided into six experimental groups, as follows: (1) one hour hypothermia, respiration supported; (2) one hour hypothermia, respiration unsupported; (3) six hours hypothermia, respiration supported; (4) six hours hypothermia, respiration unsupported; (5) twelve hours hypothermia, respiration unsupported; (6) eight normothermic dogs with respiration unsupported for twelve hours, were employed as controls.

All dogs were anæsthesized by injecting intravenously 28mg of pentobarbital sodium per kilogram of body weight. Supplementary dosages of anæsthetic were administered when required to maintain a surgical level of anæsthesia throughout the experimental period. The additional dosages were: group (3) 15 per cent of original; (4) 10–40 per cent; (5) 50 per cent; (6) 30–100 per cent.

Thirty minutes after induction of anæsthesia the dogs were immersed in an ice water bath until their sigmoid temperatures dropped to 28°C, and after one hour were further cooled to 25–26°C. This temperature range was maintained by wetting the animal with ice water, or drying and covering with a wool blanket, as was demanded. In general, the animals were hypothermic two to three hours longer than the defined

experimental period because of time spent in protracted cooling and rewarming. The animals were rewarmed in water at 40–43°C.

Supported respiration consisted of placing the dogs on an intermittent positive pressure respirator from which they received air (not oxygen). The animals were removed from the respirator immediately following rewarming.

Temperature and respiration were determined at half-hour intervals while the hypothermic state persisted.

Blood samples were heparinized in order to obtain plasma since difficulty was experienced obtaining unhemolyzed serum. Hemolysis must be avoided because erythrocytes contain the enzyme. Samples were obtained by venepuncture in syringes treated with just enough mineral oil so that the plunger worked freely. Immediately after withdrawing 3–6ml, the blood was transferred to a tube and centrifuged, after which the plasma was withdrawn and stored at 5°C or frozen. After a few days' refrigeration, a fibrin clot was usually formed, hence the assays were actually performed on serum. Karmen[18] states that there are no significant differences in transaminase activity of serum or heparinized plasma.

Control blood samples were secured from all animals half-an-hour after induction of anæsthesia but prior to immersion. Samples from animals in groups (1), (3) and (5) were obtained one-half hour after they were on the respirator. Samples from all animals were secured twenty-four, forty-eight and seventy-two hours after rewarming and in certain instances eight, twelve, sixteen and twenty hours post-hypothermia.

The transaminase assays were performed using a Beckman Model B spectrophotometer, according to the method of Karmen [18], as outlined by Steinbert *et al*[19].

RESULTS

The results of the transaminase assay are presented in TABLES 1 through 5. The mean SGOT activity for the 48 control samples listed in TABLES 2, 3 and 4 is 17 units per ml, with a range of 9–25 units per ml. The twenty-four hour samples proved to be the most critical. They were late by eight to twelve hours from the times of peak elevation as shown by the more frequent sampling data presented in TABLE 5. However, they do reveal significant elevations.

The SGOT activity of the sixteen dogs subjected to one hour of hypothermia, with and without supported respiration remained within 7 units per ml of the control range. One sample showed marked hemolysis and exhibited greater activity.

Of the eight dogs hypothermic for six hours with respiration supported, six had SGOT activities within 10 units per ml of control

values. The other two showed elevations at twenty-four hours up to 230 per cent above control. Five of the eight dogs without supported respiration exhibited elevations 560 per cent above the normal range. The remaining animals in this group died of respiratory failure.

All the animals hypothermic twelve hours with supported respiration, exhibited marked elevations (by a factor of 4.3) in transaminase activity twenty-four hours post warming. However, all were within the control range seventy-two hours after rewarming. Only three dogs with unsupported respiration survived the twelve hours hypothermia, and these died twenty-five to thirty hours following rewarming and showed increased transaminase activities (by a factor of nine above controls). Similarly treated normothermic animals (TABLE 1) survived with no significant changes in SGOT activity (two hæmolysed samples had increased activities).

DISCUSSION

Transaminase activity reaches a maximum a few hours after acute tissue injury and if no additional trauma results, returns to control values in a day or so. Agress[13] found peaks at nine and twenty-three hours following experimentally-produced myocardial infarction. In the present study, three of the eight dogs subjected to six hours of hypothermia (respiration unsupported), were sampled and assayed for SGOT activity eight, twelve, sixteen and twenty hours after rewarming (TABLE 5). A plot of transaminase activity against time shows peak values occurring sixteen to twenty hours after rewarming.

The sixteen animals hypothermic one hour showed no severe tissue damage according to the criterion of SGOT activity. It appears that surface immersion cooling, one hour at 25–26°C, and surface immersion rewarming in 40–43°C water, does not produce severe damage to transaminase-rich tissues of dogs. The statement should be qualified because of the possibility that cell injury could have occurred which is not drastic enough to release transaminase, or tissues may be selectively damaged, but low in transaminase content.

The eight dogs hypothermic six hours with supported respiration, exhibited no tissue damage comparable to that of infarctions in which SGOT activities of 100–300 units per ml are not uncommon. By the SGOT criterion, it appears that six hours of hypothermia with supported respiration *per se* is not particularly injurious. The evidence is inconclusive, however, as to whether or not it might be somewhat more injurious than one hour cooling.

It is quite obvious (TABLES 2, 3 and 4) that in prolonged hypothermia, ventilation plays a significant role. Of those animals hypothermic six hours without supported respiration, 37 per cent succumbed of respiratory failure, whereas twelve hours hypothermia

resulted in death to 62 per cent of the animals. Likewise, the longer the hypothermia, the greater the increase in transaminase activity (six hours, by a factor of 5.6 above controls; twelve hours, by a factor of 9.0 above controls at twenty-four hours).

Russ[20 21] reported that after eighteen hours of hypothermia, as the cardiac index decreases, there is an increase in the coefficient of oxygen utilization and a concomitant increase in plasma transaminase. These workers have also shown that as the hours of hypothermia are prolonged, the blood supply to the liver and other tissues is diminished and during the latter stages becomes inadequate. This condition presumably leads to severe tissue hypoxia and subsequent tissue damage with release of transaminase.

Table 1

Transaminase activity following twelve hours normothermia

Respiration unsupported

	RESPIRATION RATE		UNITS TRANSAMINASE PER ML PLASMA			
			BEFORE	HOURS POST-WARMING		
DOG	MEAN	MINIMUM	ANESTHESIA	*24*	*48*	*72*
1A	14	6	17	11	14	18
2A	36	7	17	15	16	15
3A	40	9	12	147M	55S	23
4A	17	7	13	21	21	10
5A	27	11	15	12	13	18
6A	18	6	16	30	14	15
7A	33	9	15	18	16	18
8A	25	7	18	19	17	17

Visible hæmolysis in sample: S, slight; M, marked

Table 2

Transaminase activity following one hour hypothermia

1 Respiration unsupported

	MINIMUM RATE OF	UNITS TRANSAMINASE PER ML PLASMA BEFORE	FOLLOWING	HOURS POST WARMING		
DOG	RESPIRATION	HYPOTHERMIA	REWARMING	*24*	*48*	*72*
1B	6	20	20	21	20	19
2B	4	20	14	15	14	17
3B	4	13	16	15	17	16
4B	16	17	15	14	116M	18
5B	10	15	19	17	18	15
6B	7	17	17	20	32S	18
7B	5	22	20	17	21	20
8B	5	19	21	14	17	18
		2 Respiration Supported				
9B		14	22	17	19	17
10B		14	15	19	18	28S
11B		22	18	13	15	14
12B		14	18	20	20	17
13B		17	15	16	13	16
14B		18	14	14	15	25S
15B		24	20	17	18	14
16B		18	21	20	19	19

Visible hæmolysis in sample: S, slight; M, marked

Table 3

Transaminase activity following six hours hypothermia

1 Respiration unsupported

			UNITS TRANSAMINASE PER ML PLASMA			
	RESPIRATION RATE		BEFORE	HOURS POST-WARMING		
DOG	MEAN	MINIMUM	HYPOTHERMIA	*24*	*48*	*72*
1C	5	3	16	42	21	17
2C	3	1	20	214s	114	15
3C	3	2	16	84	76	22
4C	3	3	12	133s	79	19
5C	4	2	14	60	60	22
6C	3	0	13	x		
7C	7	3	19	54	44	17
8C	2	0	9	x		
			2 Respiration supported			
9C			16	17	14	16
10C			21	60	22	17
11C			10	30	20	20
12C			17	31	28	20
13C			22	35	24	18
14C			18	21	20	21
15C			17	54	18	16
16C			11	14	12	10

Visible hæmolysis in sample: s, slight
x died of respiratory failure during hypothermia

Table 4

Transaminase activity following twelve hours hypothermia

1 Respiration unsupported

			UNITS TRANSAMINASE PER ML PLASMA			
	RESPIRATION RATE		BEFORE	HOURS POST-WARMING		
DOG	MEAN	MINIMUM	HYPOTHERMIA	*24*	*48*	*72*
1D	3	0	16	x		
2D	5	2	16	166	xx	
3D	4	0	14	x		
4D	9	4	18	155	xx	
5D	5	1.5	16	184	xx	
6D	3	0	25	x		
7D	4	0	21	x		
8D	3	0	13	x		
			2 Respiration supported			
9D			21	88	24	18
10D			19	117	36	21
11D			21	136	26	25
12D			18	89	20	19
13D			15	123	21	18
14D			22	77	20	18
15D			14	65	31	21
16D			14	74	22	15

x Died of respiratory failure during hypothermia
xx Died between twenty-five and thirty hours post-warming

Table 5

Transaminase activity at various intervals following six and twelve hours hypothermia, respiration unsupported

UNITS TRANSAMINASE PER ML PLASMA

	BEFORE	HOURS POST-REWARMING				
DOG	HYPOTHERMIA	*8*	*12*	*16*	*20*	*24*
3C x	16	48	68	117	94	84
5C	14	59	72	200	89	60
7C	19	31	88	167	78	54
2D xx	15	66	179	236	194	166
4D	18	83	146	229	172	155
5D	17	54	185	302	197	184

x From TABLE 3
xx From TABLE 4

SUMMARY

Serum glutamic oxalacetic transaminase (SGOT) activities were determined in dogs subjected to various periods of hypothermia, with and without supported respiration.

One or six hours of hypothermia with supported respiration had little effect on SGOT activities, however, twelve hours of hypothermia with respiration supported, resulted in significant changes in SGOT activity beginning twelve hours following rewarming, but returning to control values thirty-six hours later.

The influence of ventilation was most markedly demonstrated in animals subjected to six or twelve hours of hypothermia. Without respiration supported, 37 per cent of the animals hypothermic six hours succumbed, whereas 62 per cent succumbed following twelve hours hypothermia.

Peak transaminase activities were detected sixteen to twenty hours following rewarming in animals subjected to six and twelve hours hypothermia, respiration unsupported.

Acknowledgements

The author wishes to acknowledge the excellent technical assistance of Philip E. Griffin and Robert H. Owen, as well as the helpful discussions with Dr E. M. Brophy, Dr W. W. Cleland, Dr C. Russ and L. P. Wendel.

A portion of this study was performed while the author was at the U.S. Army Medical Research and Nutrition Laboratory, Denver, Colorado.

References

[1] BIGELOW, W. G., LINDSAY, W. K. and GREENWOOD, W. F. (1950). Hypothermia; its possible role in cardiac surgery: An investigation of factors governing survival in dogs at low body temperature. *Ann. Surg.*, *132*, 849.

[2] SWAN, H., ZEAVIN, I., HOLMES, J. H. and MONTGOMERY, V. (1953). Cessation of circulation in general hypothermia: 1. Physiologic changes and their control. *Ann. Surg.*, *138*, 360.

[3] KNOCKER, P. (1955). Effects of experimental hypothermia on vital organs. *Lancet*, *2*, 837.

[4] FALKNER, S. and KJELLGREN, K. (1955). Morphologic and functional changes under hypothermia. *Acta. Soc. Med. Upsal.*, *60*, 199.

[5] SARAJAS, H. S. S. and NILSSON, T. E. (1954). Beobachtungen über die Pathologie der experimentellen Hypothermie beim Hunde. *Verhandl. deutsch. Gesellsch. inn. Med.*, *60*, 118.

[6] BLAIR, E., MONTGOMERY, A. V. and SWAN, H. (1956). Posthypothermic circulatory failure: 1. Physiologic observations on the circulation. *Circulation*, *13*, 909.

[7] DETERLING, R. A., JR., NELSON, E., BHONSLAY, S. and HOWLAND, W. (1955). Study of basic physiologic changes associated with hypothermia. *A.M.A. Arch. Surg.*, *70*, 87.

[8] ROSS, D. N. (1954). Hypothermia: Physiological observations during hypothermia. *Guy's Hosp. Rep.*, *103*, 116.

[9]WROBLEWSKI, F. (1959). The clinical significance of transaminase activities of serum. *Am. J. Med., 27*, 911.

[10]WENDEL, O. W. and CHARKEY, L. W. (1958). Influence of environmental temperature and chlorpromazine on biochemical changes following bowel shock. *Proc. Soc. Exper. Biol. and Med., 98*, 463.

[11]LADUE, J. S., WROBLEWSKI, F. and KARMEN, A. (1954). Serum glutamic oxalacetic transaminase activity in human acute transmural myocardial infarction. *Science, 120*, 497.

[12]STEINBERG, D. and OSTROW, B. H. (1955). Serum transaminase as a measure of myocardial necrosis. *Proc. Soc. Exper. Biol. and Med., 89*, 31.

[13]AGRESS, C. M., JACOBS, H. I., GLASSNER, H. F., LEDERER, M., KARMEN, A., CLARK, W. G., WROBLEWSKI, F. and LADUE, J. S. (1955). Serum transaminase levels in experimental myocardial infarction. *Circulation, 11*, 711.

[14]NYDICK, I., WROBLEWSKI, F. and LADUE, J. S. (1955). Evidence for increased serum glutamic oxalacetic transaminase activity following graded myocardial infarcts in dogs. *Circulation, 12*, 161.

[15]RUDOLPH, L. A., SCHAEFER, J. A., DUTTON, R. E., JR. and LYONS, R. H. (1957). Serum glutamic oxalacetic transaminase in experimental tissue injury. *J. Lab. Clin. Med., 49*, 31.

[16]LADUE, J. S. and WROBLEWSKI, F. (1955). The significance of the SGOT activity following acute myocardial infarction. *Circulation, 11*, 871.

[17]NICKELL, W. K. and ALLBRITTEN, F. F. (1957). Serum transaminase content related to tissue injury. *Surgery, 42*, 240.

[18]KARMEN, A. (1955). A note on the spectrophotometric assay of glutamic oxalacetic transaminase in human blood serum. *J. Clin. Invest., 34*, 131.

[19]STEINBERG, D., BALDWIN, D. and OSTROW, B. H. (1956). A clinical method for the assay of serum glutamic oxalacetic transaminase. *J. Lab. Clin. Med., 48*, 144.

[20]RUSS, C. and MCCOLLESTER, K. (1959). Plasma transaminase levels as an index of tissue hypoxia during prolonged hypothermia. *Fed. Proc., 18*, 132.

[21]RUSS, C. Personal communication.

The effect of halothane (fluothane) on the thalamus and midbrain reticular formation*

HAMILTON S. DAVIS, MD

Assoc. Prof. of Anesthesiology

VINCENT E. QUITMEYER, MD

Instructor in Anesthesiology

WILLIAM F. COLLINS, MD

Assoc. Prof. of Neurosurgery
Western Reserve University School of Medicine and the University Hospitals, Cleveland 6, Ohio

Emerging as an important anæsthetic agent in the past few years, halothane (fluothane) has undergone many clinical and laboratory investigations. These studies have been directed primarily toward its circulatory and respiratory effects. There have been a few studies of its central nervous system effects with regard to the electroencephalographic changes associated with varying depths of anæsthesia[1,2]. The work of French, Verzeano and Magoun[3] has more recently focused attention on the actions of anæsthetics at subcortical levels, particularly on the 'reticular activating system' of the midbrain core. To our knowledge, the effects of halothane on this region have not yet been reported.

The present study describes in the cat the effects of halothane on evoked responses in the postero-ventrolateral (PVL) nucleus of the thalamus – representing a relay point in the classical lateral afferent systems – and in the reticular formation (RF) of the midbrain at the level of the superior colliculus, representing a point in the indirect central afferent system. Results obtained point to a response similar qualitatively, but different quantitatively, to that obtained by previous studies in this laboratory with other commonly used volatile anæsthetic agents[4].

*Aid in part by Grant B779 (C_5) from National Institute of Neurological Diseases and Blindness, Washington, DC.

METHODS

Fifteen adult cats were studied. The experimental method, described fully in a previous publication[5], consisted of stereotaxically placing two stainless steel electrodes (insulated to within 60–150 microns of their 15 micron diameter tips) into the selected subcortical regions of cats anæsthetised with cyclopropane and subsequently recording the responses evoked at these two points by an electrical stimulus applied to a peripheral sensory nerve after replacing cyclopropane with halothane.

A tracheotomy was done initially through which mechanical artificial ventilation was maintained in a to-and-fro absorption circuit. A femoral vein and artery were canulated for administering fluids and drugs and monitoring the arterial blood pressure with an electromanometer respectively. Subcutaneous needle electrodes provided a lead 1 electrocardiogram. The rectal temperature was followed by a mercury thermometer. A superficial radial nerve was exposed and a bipolar stimulating electrode applied to it. A contralateral hemicraniectomy was performed. At this point, all surgery being completed, the animal's hind limbs were elevated, it was immobilised by intravenous gallamine (flaxedil) 4–8mg/kg, the cyclopropane shut off and artificial ventilation with oxygen substituted. Throughout the experiment, to avoid the devasting effects of hypoxia on the potentials under observation, minute volumes of 1500–3000ml (N=322ml[6]) were delivered. The resultant hyperventilation produced no apparent adverse effects.

After forty-five minutes of oxygen, the recording electrodes were inserted by a micromanipulator into the contralatercal thalamic PVL nucleus and the midbrain RF locus at appropriate co-ordinates[7] and stimulation of the nerve begun at three second intervals with 1–3 volt square wave impulses of 0.5 millisecond duration. The resultant evoked potentials in the two regions were passed through cathode followers, amplified and projected on a synchronised dual beam oscilloscope, whence they were photographed. After manipulation yielded maximum evoked potentials of characteristic form and latency for the two regions, the electrodes were locked in position. The positions of the tips were later verified histologically[8].

After a steady state was achieved and control tracings photographed, halothane was applied in concentrations varying from 0.25–2.0 per cent. Each run, during which the anæsthetic* was administered by

* Desired vapor concentrations were obtained by voltatilising a known volume of halothane with a proper volume of oxygen, as determined by the usual gas equations[9]. The oxygen flow was measured by means of a standard Foregger rotameter recalibrated for accuracy.

manually controlled ventilation using a Stephen-Slater valve from a small breathing bag fed by the gas from a 40 litre latex reservoir, lasted a minimum of eleven minutes with potentials being photographed at one to two minute intervals. Upon completion of each halothane run, oxygen was substituted at flows of 3 litres per minute and potentials recorded at one to five minute intervals until control levels of responses returned. This sequence was repeated for several concentrations of the anæsthetic in each animal.

Hypoxia and hypothermia were assiduously avoided in all instances because of their known depressant effects on the regions under observation. Hypotension was usually avoided by elevation of the hind limbs; however, not infrequently the higher concentrations of halothane produced significantly lowered blood pressures necessitating intravenous infusion of either phenylephrine (neosynephrin) or norepinephrine (levophed) to restore normal levels.

In two instances, intact animals were anæsthetised with varying halothane-oxygen concentrations in a plastic chamber[10] and their behaviour observed throughout. They were subsequently subjected to the usual test preparation with, in addition, conventional electroencephalographic recordings taken from bipolar occipito-frontal leads.

RESULTS

FIG. 1 shows representative recordings obtained from this type of preparation. The thalamic PVL response is characterised by a spike-like

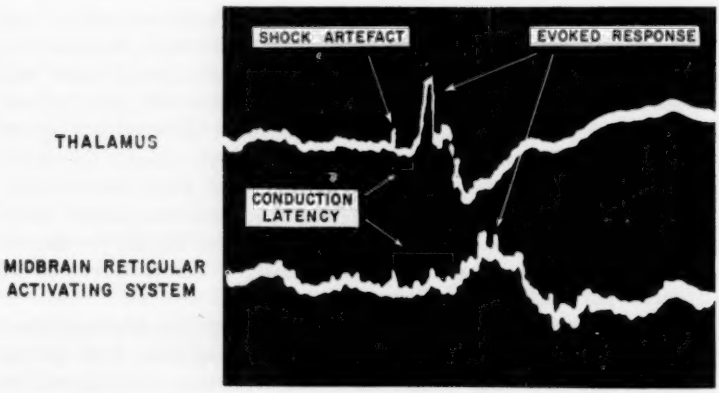


FIG. 1 Examples of evoked responses from the nucleus posteroventrolateralis (PVL) of the thalamus (top) and the periaqueductal reticular formation of the midbrain (bottom). (From DAVIS, COLLINS, RANDT and DILLON (1957). *Anesthesiology*, *18*, 639.)

Table 1

Amplitude of control subcortical evoked potentials in cat

ANIMAL NUMBER	ANIMAL WEIGHT IN KG	PEAK AMPLITUDE OF EVOKED POTENTIALS IN MICROVOLTS	
		THALAMUS (PVL)	MIDBRAIN (RF)
1	2.2	187	100
2	2.6	182	92
3*	—	—	—
4	2.8	313	125
5	2.6	166	63
6	2.3	183	63
7	3.5	166	88
8	2.0	206	50
9	1.7	133	81
10	2.3	331	100
11	2.0	244	145
12	1.9	256	50
13	2.4	243	90
14	1.6	114	50
15	2.8	107	52
Range	1.6–3.5	107–331	50–145
Mean ($\bar{x}$ = 14)	2.3	202	82

* Recording failure in this animal.

potential of short latency (cā 4msec) and duration, the midbrain RF by a wave of longer latency (cā 10–14msec) and duration. As indicated in TABLE 1, the mean amplitude of the thalamic potential in this study was 202 microvolts, the midbrain RF amplitude 82 microvolts. In all instances, amplitudes were determined with calipers by measuring from the base line to the peak of the response and then converting this to microvolts by comparison with calibration signals of known microvoltage superimposed on the records. The accuracy of this method is $\pm$10 per cent.

Although fifteen cats were studied, the data from fourteen only were included in the results because of one recording failure. Each animal served as its own control and all absolute amplitude values were converted into percentages of control amplitudes. These percentage values were used throughout, but one might, if desired, determine absolute values for the individual animals specifically indicated in the text by reference to TABLE 1.

The individual findings for cats 8 and 11 were considered reasonably representative and are presented in FIGS. 2, 3, 4 and 5 for halothane concentrations of 0.25 per cent, 0.5 per cent, 1 per cent and 2 per cent respectively.

In order to point out the trends in each of the four *groups* of animals subjected to different concentrations of the agent, the data are presented in the scatter-graphs in FIGS. 6, 7, 8 and 9 for halothane concentrations of 0.25 per cent, 0.5 per cent, 1 per cent and 2 per cent respectively which include not only all the individual values obtained for each animal, but also the calculated means for each group at the indicated times. It should be emphasised that the mean values plotted toward the end of each period of halothane administration are of questionable significance because of the small number of observations included.

Thus, marked deviations from the established trend of the means in several of the plots may be due to this inadequate sampling. To supplement the graphs, the mean changes are summarised in TABLE 2.

Table 2

Effect of halothane (fluothane) on subcortical evoked central nervous system responses in cat

CONCENTRATION PER CENT V/V	NUMBER OF ANIMALS*	SITE OF RECORDING OF EVOKED POTENTIALS	MEAN CHANGES IN EVOKED POTENTIALS ONSET OF SIGNIFICANT SUPPRESSION† (MINUTES)	MAXIMAL SUPPRESSION MINUTES	MAXIMAL SUPPRESSION PER CENT	MAXIMAL RECOVERY MINUTES	MAXIMAL RECOVERY PER CENT
0.25%	6	Thalamus PVL nucleus	1	11	11	25	98
		MB-periaqueductal reticular formation	2	13	38	30	100
0.5%	14	Thalamus PVL nucleus	3	21	24	35	99
		MB-periaqueductal reticular formation	1	17	55	35	88
1.0%	13	Thalamus PVL nucleus	1	17	32	35	98
		MB-periaqueductal reticular formation	1	21	79	26	84
2.0%	6	Thalamus PVL nucleus	1	17	55	30	80
		MB-periaqueductal reticular formation	1	15	91	30	59

*Total of 14 animals. Each animal was tested at several concentrations of the agent.
†'Significant' suppression arbitrarily chosen as at least 10 per cent reduction relative to control potential. No attempt made to measure changes under one minute.

Halothane 0.25 per cent

Even at the very low concentration of 0.25 per cent, halothane exerted a slight effect on the thalamic PVL nucleus and an appreciable effect on the midbrain RF, as indicated in TABLE 2 and FIG. 6, which came on rapidly and recovered slowly to control levels.

Examples of these effects in the single animal (cat 11) are seen in the reproductions of the tracings recorded at 0 minutes (control), following five minutes of halothane and twenty minutes after its removal, as shown in FIG. 2. No change in latency of either response is evident. A mild drop in blood pressure occurred during the first five minutes of the run in this animal, but in general the circulation was well-maintained without recourse to vasopressors and there were no significant cardiac arrhythmias. This was typical for this low concentration of agent.

Halothane 0.5 per cent

At the comparatively low concentration of 0.5 per cent, halothane exerted a slightly greater depressant effect on the thalamic PVL nucleus and considerable depression on the midbrain RF, as indicated in TABLE 2 and FIG. 7. The initial effects came on rapidly, the depression progressed steadily to a delayed maximum, and recovery to control levels was slow.

The graph of the single animal in FIG. 3 (cat 8) shows minimal thalamic depression, a rapidly depressed midbrain RF which leveled off to an early maximum and recovered rapidly. Tracings representing

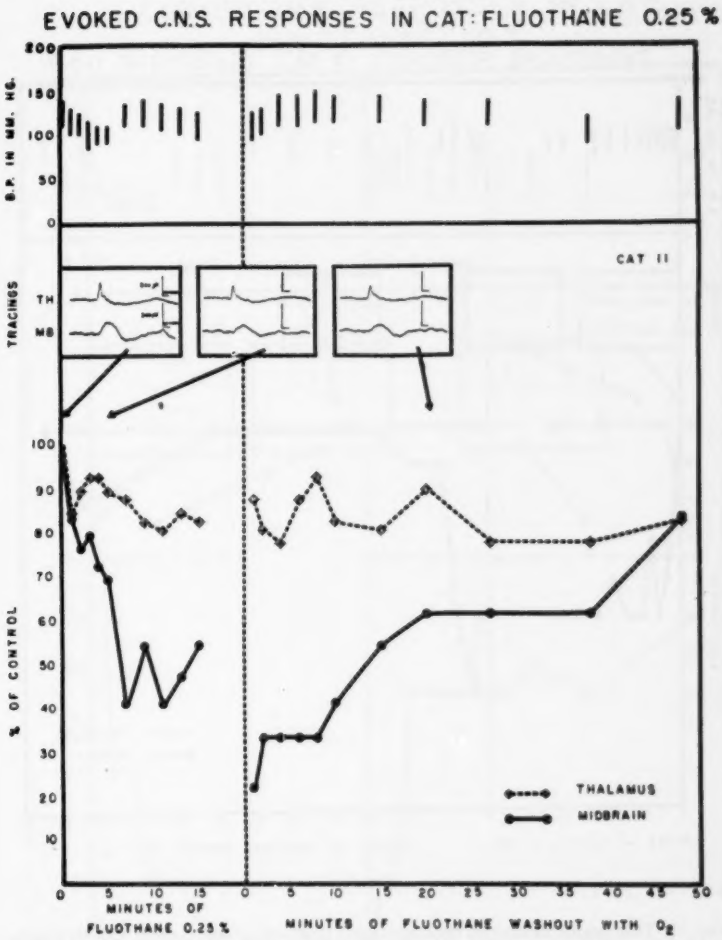


FIG. 2 This graph illustrates representative findings in one animal (cat 11) which received 0.25 per cent halothane (fluothane) in oxygen. Individual amplitudes of evoked responses, expressed as percentages of controls, are plotted at frequent intervals during administration (left) and following removal (right) of the anæsthetic mixture for the nucleus postero-ventrolateralis (PVL) of the thalamus and the periaqueductal reticular formation (RF) of the midbrain (lower section). Photographs of tracings from these two regions are superimposed (middle section) before, during and after halothane; the calibration lines indicating 300 microvolts and 10 milliseconds in the left-hand photograph also pertain to the other two photographs. Simultaneous systolic and diastolic blood pressure values are indicated at frequent intervals throughout the experiment (upper section).

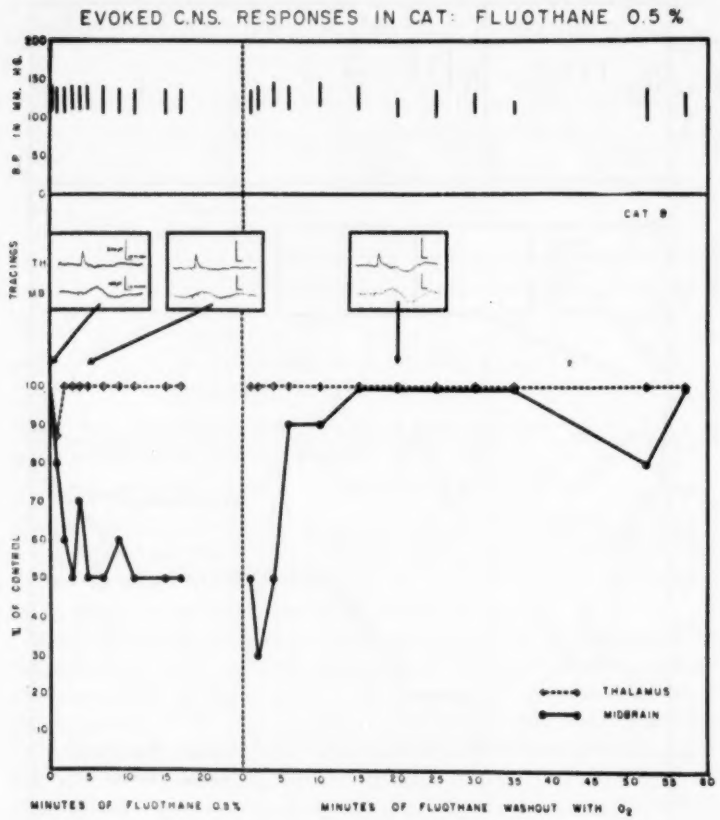


FIG. 3 This graph illustrates representative findings in one animal (cat 8) which received 0.5 per cent halothane (fluothane) in oxygen. The balance of the description beneath FIG. 2 pertains to this graph also, except for different calibration lines in the tracings (middle section), the lines in the upper thalamic tracing indicating 300 microvolts and 10 milliseconds, those in the lower midbrain tracing indicating 100 microvolts and 10 milliseconds.

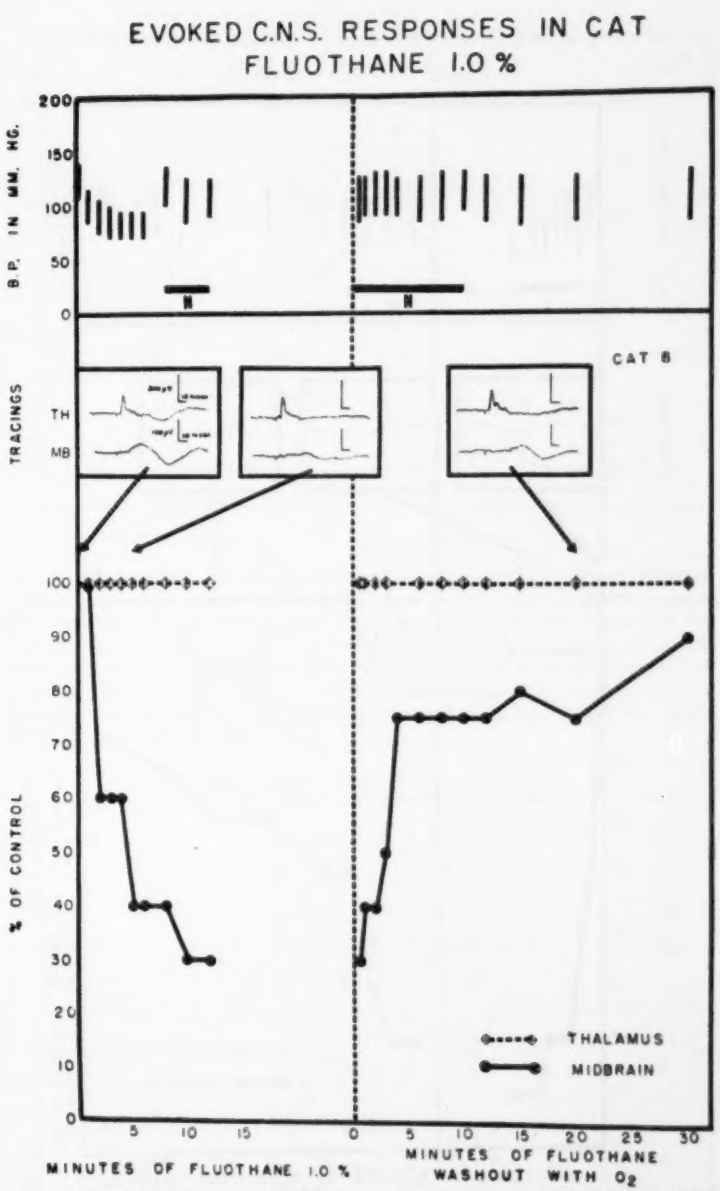


FIG. 4 This graph illustrates representative findings in one animal (cat 8) which received 1.0 per cent halothane (fluothane) in oxygen. The balance of the description beneath FIG. 2 pertains to this graph also, except for different calibration lines in the tracings (middle section), the lines in the upper thalamic tracing 300 microvolts and 10 milliseconds, those in the lower midbrain tracing indicating 100 microvolts and 10 milliseconds; and, in addition, the presence of the horizontal bars (upper section) representing the time and duration of administration of a norepinephrine (N) infusion.

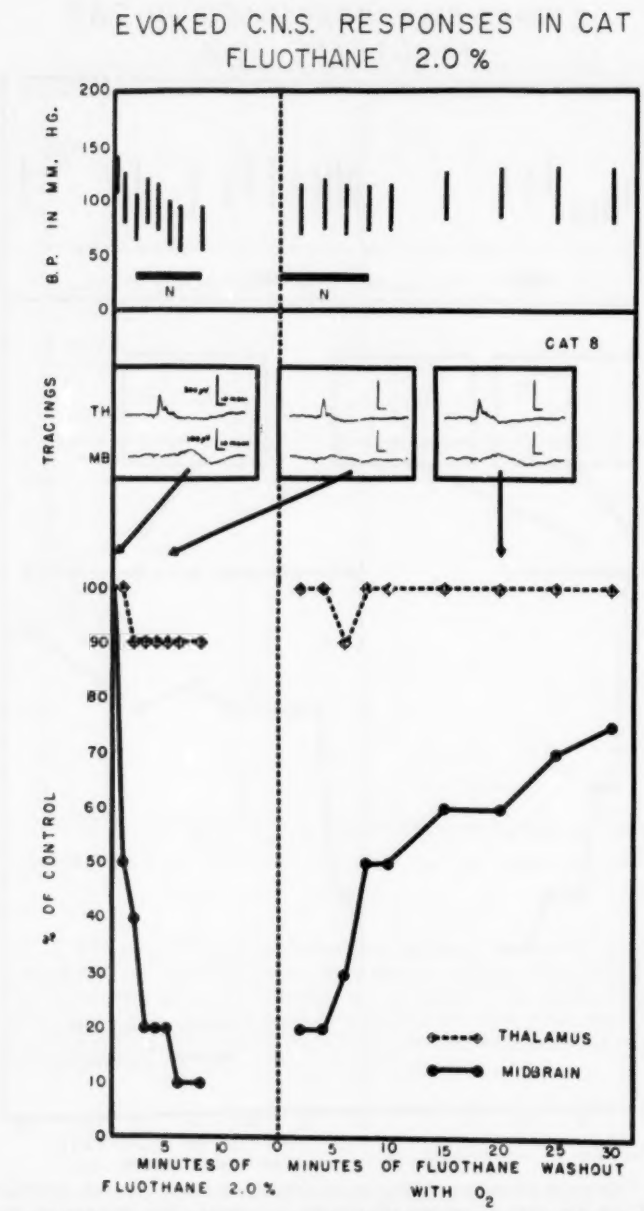


FIG. 5 This graph illustrates representative findings in one animal (cat 8) which received 2.0 per cent halothane (fluothane) in oxygen. The balance of the description beneath FIG. 2 pertains to this graph also, except for different calibration lines in the tracings (middle section), the lines in the upper thalamic tracing indicating 300 microvolts and 10 milliseconds, those in the lower midbrain tracing indicating 100 microvolts and 10 milliseconds; and, in addition, the presence of the horizontal bars (upper section) representing the time and duration of administration of a norepinephrine (N) infusion.

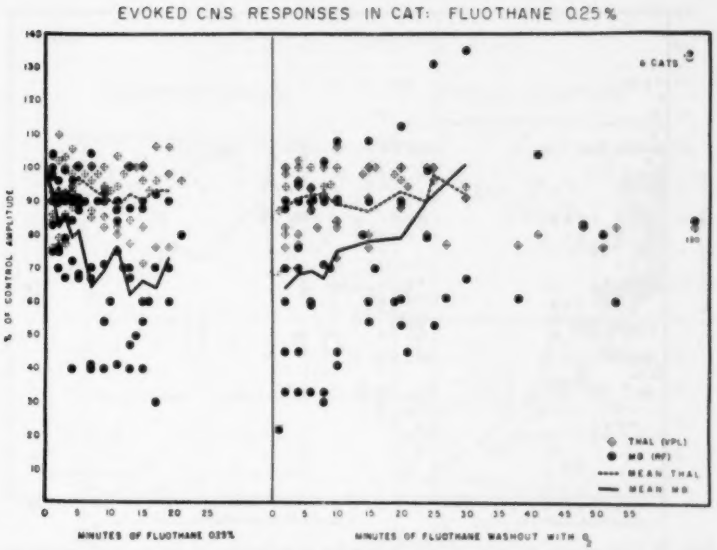


FIG. 6 This graph includes all the values for amplitudes of the evoked responses obtained at similar time intervals for each of the six animals which received halothane (fluothane) 0.25 per cent in oxygen. The individual values for the responses of the thalamic PVL nucleus and the midbrain RF are plotted at frequent intervals during (*left*), and following (*right*) administration of the anæsthetic mixture. The means of the responses grouped at the various time intervals were calculated, and are superimposed as points joined by dotted (thalamic) and solid (midbrain) lines.

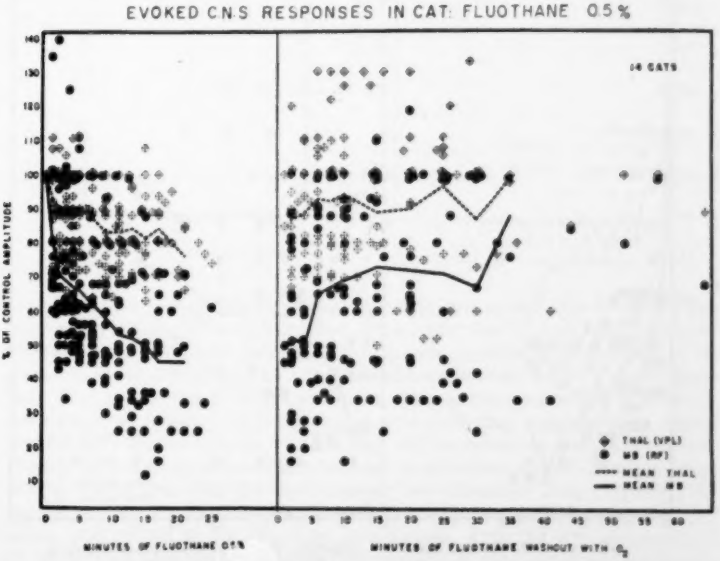


FIG. 7 This graph includes all the values for amplitudes of the evoked responses obtained at similar time intervals for each of the fourteen animals which received halothane (fluothane) 0.5 per cent in oxygen. The balance of the description beneath FIG. 6 pertains to this graph also.

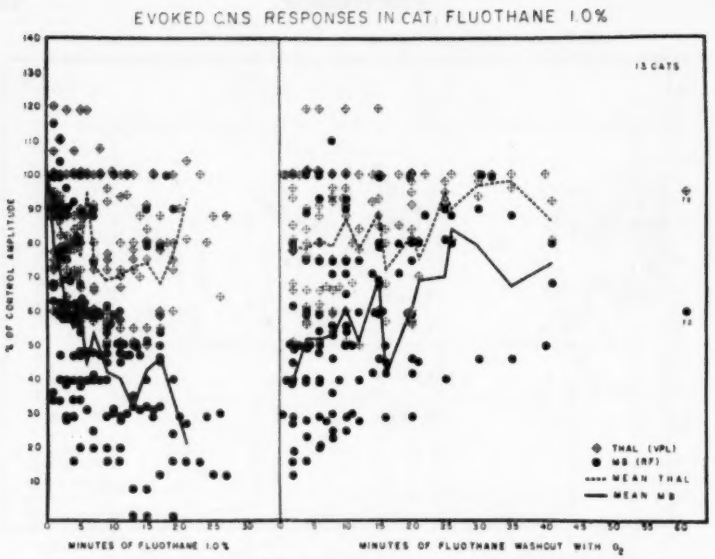


FIG. 8 This graph includes all the values for amplitudes of the evoked responses obtained at similar time intervals for each of the thirteen animals which received halothane (fluothane) 1 per cent in oxygen. The balance of the description beneath FIG. 6 pertains to this graph also.

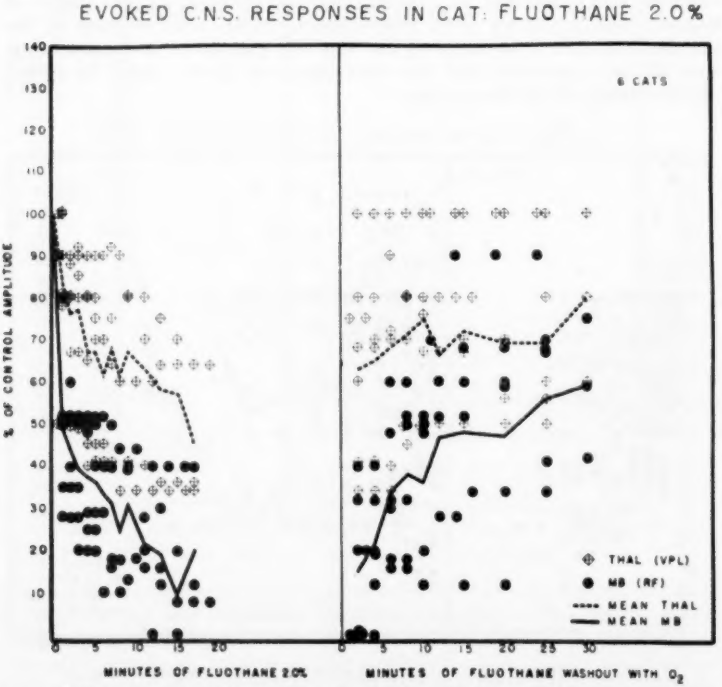


FIG. 9 This graph includes all the values for amplitudes of the evoked responses obtained at similar time intervals for each of the six animals which received halothane (fluothane) 2 per cent in oxygen. The balance of the description beneath FIG. 6 pertains to this graph also.

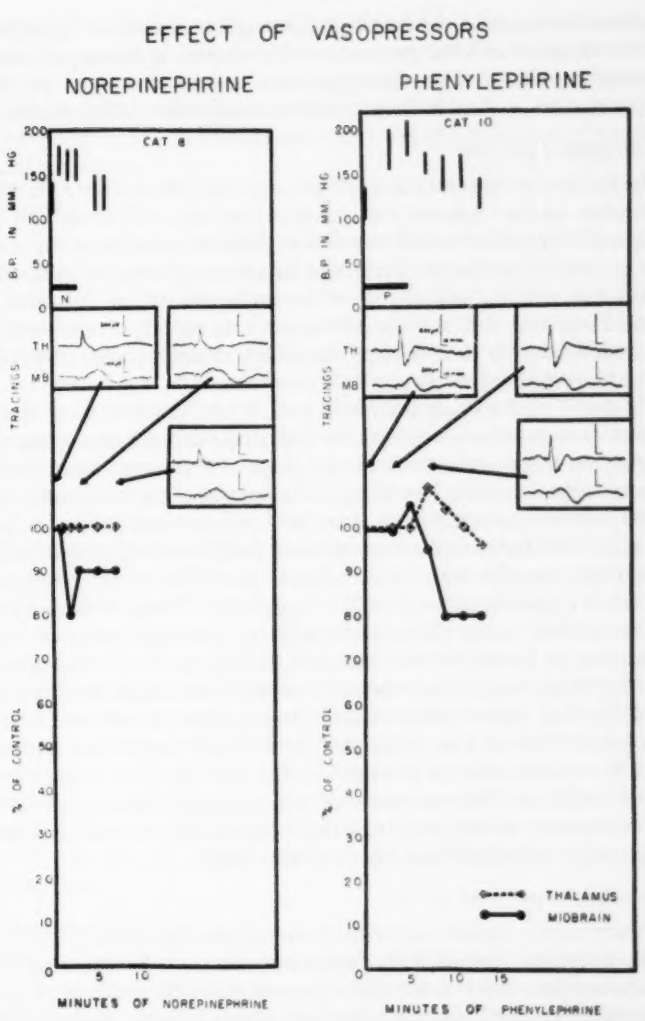


FIG. 10 These two graphs illustrate findings in one animal (cat 8, *left*), which received an infusion of norepinephrine, and another (cat 10, *right*) which received phenylephrine in a similar manner. The times and duration of these infusions are indicated by the horizontal bars (upper sections) marked N and P respectively. Individual amplitudes of evoked responses, expressed as percentages of controls, are plotted at frequent intervals during and following administration of the vasopressors for the thalamic PVL nucleus and the midbrain RF (lower section). Photographs of tracings from these two regions are superimposed (middle section) before, during and after the vasopressors; the calibration lines indicating 300 microvolts and 10 milliseconds, in the left-hand photograph of the left-hand graph, also pertain to the other two photographs, while the 400 microvolt and 10 millisecond lines, in the left-hand photograph of the right-hand graph, also pertain to the remaining two photographs of that graph. Simultaneous systolic and diastolic blood pressure values are indicated at frequent time intervals throughout each of the two experiments (upper sections).

these events are seen at 0 minutes, following five minutes of halothane and twenty minutes after its removal. No change in latency of either response is evident. The blood pressure was unaffected as was the cardiac rhythm, typical findings at this concentration of halothane.

Halothane 1 per cent

At the moderate concentration of 1 per cent, halothane exerted further depression on the thalamic PVL nucleus (the sudden lessening in the pattern of depression at six minutes is difficult to account for; that seen at twenty minutes is likely due to sampling error as described above) and marked depression of the midbrain RF, as indicated in TABLE 2 and FIG. 8. The initial effects came on rapidly, the depression progressed steadily to a delayed maximum, recovery was slow and, for the midbrain, incomplete in thirty minutes.

The graph of the single animal in FIG. 4 (cat 8) shows a rapid and progressively depressed midbrain RF reaching a delayed maximum and a rapid, but incomplete recovery. Tracings of these events are seen at the usual time intervals. No change in latency of either response is evident. There was an appreciable drop in blood pressure during the first five minutes of halothane administration which was supported with a norepinephrine drip. Six of the thirteen cats in this group developed significant hypotension requiring a vasopressor. Three of these hypotensive animals were given phenylephrine infusions with prompt restoration of normal blood pressures and no cardiac arrhythmias; the other three received norepinephrine infusions which restored the blood pressure, but in each instance led to cardiac arrhythmias varying from nodal rhythms and occasional Wolfe-Parkinson-White patterns of aberrant conduction to premature ventricular systoles. These cleared with cessation of the vasopressor even when halothane was continued; conversely, norepinephrine alone produced hypertension, but no arrhythmias until halothane 1 per cent was added.

Halothane 2 per cent

Representing the highest concentration used in this study, 2 per cent halothane exerted considerable depressant effects on the thalamic PVL nucleus and just short of complete depression of the midbrain RF, as indicated in TABLE 2 and FIG. 9. (The sudden increase in depression of the thalamus and decrease in the midbrain depression seen at seventeen minutes in FIG. 9 is likely a sampling error.) The initial effects were rapid with a steady progression to a delayed maximum depression and recovery was slow and incomplete in thirty minutes.

In the graph of a single experiment in FIG. 5 (cat 8), the usual tracings of these events are seen. No change in latency of either response is evident. There was an appreciable blood pressure drop re-

quiring norepinephrine. Five of the six cats in this group developed severe hypotension after halothane was begun. The infusion of norepinephrine corrected this hypotension, but produced significant arrhythmias of the types mentioned above. Removal of either the norepinephrine or the halothane promptly led to restoration of a normal cardiac rhythm.

Vasopressors

Early in this study it was obvious that halothane in concentrations of 1 per cent or greater, produced significant hypotension in a majority of animals. It became almost routine to support the circulation, particularly in the 2 per cent group, with either phenylephrine or norepinephrine infusions. Although it was felt that these vasopressors had no significant effect on the evoked responses being studied, it was decided to check this impression. Accordingly, after steady states were obtained with oxygen alone, two animals were infused with phenylephrine and three with norepinephrine for periods up to six minutes, followed by observation over a five to fifteen minute period.

The results were variable, but, in general, the *phenylephrine* had no significant effect on either thalamic or midbrain potentials *during* administration, but there was either slight stimulation or depression of the thalamus and slight depression of the midbrain RF *after* the drug was discontinued. This effect is demonstrated in one animal, cat 10 (right-hand graph of FIG. 10) along with the blood pressure levels attained during the experiment. The *norepinephrine* similarly showed no effect on the thalamus *during* administration while there was slight depression of the midbrain RF; *after* the drug was discontinued, the thalamus showed either a slight stimulation or depression while the midbrain showed a slight, but consistent depression. The left-hand graph of FIG. 10 illustrates the findings in cat 8 given norepinephrine. Neither drug at any time showed any detectable change in the latency of response.

Intact animals

The tests carried out on intact animals with 0.5 per cent and 1 per cent halothane in oxygen were of considerable interest. In both animals so studied (cats 14 and 15), 0.5 per cent halothane produced ataxia in a few minutes, then drowsiness from which state they could be aroused by slapping the chamber walls during the ten minute exposure. The electroencephalograms of these two animals, taken a few days later while they were undergoing the usual evoked response experiments, initially showed alert control patterns of 20–30cps, 20–100 microvolt activity which gave way after four to five minutes of 0.5 per cent halothane to a tracing characterised by bursts of 8–10cps, 200–250

microvolt 'sleep spindles', which persisted over the seventeen to nineteen minute exposure to the anæsthetic, and returned to alert control patterns ten minutes after halothane was discontinued.

At the 1 per cent halothane level, the animals became ataxic in one to two minutes and fell into deep sleep shortly, thereafter, from which they could not be aroused even by shaking the chamber during the ensuing five to ten minute exposu- They awoke in approximately the same period of time as it took to sthetise them and then remained ataxic for another eight to ten mi tes. The electroencephalograms showed occasional sleep spindles in one to four minutes, progressing to frequent bursts and generally slow activity in a few more minutes, this pattern persisting throughout the remainder of the seventeen minute run. Following removal of the anæsthetic, the sleep spindles gradually disappeared over the next twenty minutes, with control activity patterns re-established in thirty-five minutes or longer.

Reference to the midbrain potentials of these two animals under the effects of 0.5 per cent and 1 per cent halothane showed both of them to be slightly less depressed at all times during administration and recovery than the means plotted in FIGS. 7 and 8.

DISCUSSION

The effects of halothane on the lemniscal afferent pathways of the cat in the regions of the thalamic PVL nucleus and on the reticular activating system in the periaqueductal region of the midbrain, are characterised by depression in their respective evoked responses, more marked in the midbrain than in the thalamus. These results are qualitatively similar, but quantitatively different from those previously found in this laboratory for the commonly used gaseous and volatile anæsthetic agents[4, 5]. The depression in the evoked activity of the reticular activating system is similar to that originally demonstrated during the anæsthetic state by French, Verzeano and Magoun[3].

From the data obtained in this study, certain conclusions are reasonable. If one superimposes the graphs of FIGS. 6, 7, 8 and 9, representing respectively the effects of halothane 0.25 per cent, 0.5 per cent, 1 per cent and 2 per cent on the evoked potentials of the two regions studied and compares the courses of the lines joining the means of these grouped values, there is seen the correlation between progressive depression of the central nervous system activity and increasing concentration of the agent, for *both* the thalamus and the midbrain. The recovery phase tends to follow roughly the same pattern of correlation although somewhat less strikingly.

This is of interest for it indicates – at least with this agent – that the lemniscal system is depressed in a fashion similar to the reticular

activating system, although to a lesser degree. There is support for this finding in the data of Haugen and Melzack who described depression of the contralateral trigemino-bulbo-thalamic path and its thalamic projection nucleus with nitrous oxide in the cat[11]; in Marshall's work with the lemniscal system of cats under deep pentobarbital[12]; in Jarcho's work with cortical afferent systems in cats under pentobarbital[13]; and in the studies of King *et al.* showing alteration of the thalamic relay in the lemniscal pathway by barbiturates in the cat[14]. On the other hand, French *et al.* reported no depression of the lemniscal portion of the sensory pathways in cats, as did Kitahata using methods virtually identical with our own[15]. Examination of the latter's data suggests that there is either a difference inherent in the agents used or in the points being studied. It also appears that different recording systems are being employed, for the latencies, amplitudes and waveforms of his evoked responses are at variance with ours for the thalamic PVL nucleus. Thus our data may not be strictly comparable.

The observations of the two intact cats under halothane showed good correlation between behavioural and neurophysiological patterns. The one discrepancy noted was a longer recovery period of the evoked responses as compared to behavioural recovery in the intact animals. This discrepancy, previously noted with cyclopropane[5], is not readily explained.

As with the other volatile agents[4], halothane showed no effect on the conduction latency – the interval between application of the stimulus to the peripheral nerve and the onset of the evoked response – at either the thalamic or midbrain points. Thus, there was no apparent effect of this agent on either the conduction velocity of the nerve fibres or the one or two synapses involved in the pathway leading into the thalamus or midbrain reticular formation.

Comparison with the findings for other volatile agents[4] indicates that the onset of depression of evoked responses is faster and that recovery is slower, although this latter difference is quite possibly due to the longer exposure times used in the halothane experiments. This slow recovery time is surprising in light of the usual rapid recovery under clinical conditions.

Any attempt to compare the anæsthetic potencies of halothane and other volatile agents by means of this study would be unwise for the experiments were not designed to yield this information. The degree of absolute depression resulting during these studies is a function not only of agent potency, but also of effective exposure time, which varied considerably in the present study when compared with earlier work involving other agents[4 5]. However, despite these variations in technique, it is apparent that there is no consistent correlation in these

studies between depression of either thalamic or midbrain evoked responses and alleged analgesic properties of anæsthetic agents. For example, ether at concentrations of 4–8 per cent produces minimal thalamic and marked reticular activating evoked response depression and at the same time will produce sleep in cat and man with no response to a skin incision. On the other hand, halothane at 1 per cent concentration produces moderate thalamic and marked reticular activating evoked response depression, at a time when a vigorous response to such a skin incision is virtually certain and, in fact, may occur at twice this concentration.

This suggests that, if the clinical impression of the analgesic potency of an agent is significant – and we feel it is – alteration in the activity of either the lemniscal pathway and/or reticular activating system does not necessarily indicate analgesic properties of the agent. It further suggests that in cats the main pain pathways are not the lemniscal or reticular activating system. Studies of the effects of different agents with varying analgesic, sedative and anæsthetic characteristics on these and other central nervous system pathways are continuing in this laboratory in the hope of defining the elusive neuropharmacological mechanisms of analgesia, as well as to define further the properties and neural mechanisms of the anæsthetic state.

SUMMARY

The effects of 0.25 per cent, 0.5 per cent, 1 per cent and 2 per cent halothane (fluothane) anæsthesia on evoked responses in the posteroventrolateral nucleus of the thalamus and the periaqueductal reticular formation of the midbrain tegmentum have been studied in fifteen adult cats. The effects of this newer volatile agent on these two regions are qualitatively similar, although quantitatively different, from those found in earlier studies involving diethyl ether, divinyl ether, trichlorethylene and chloroform. Specifically, halothane depressed both regions with the midbrain point showing by far the more marked effect.

These findings add support to the concept that a reversible depression of the midbrain reticular activating system is of primary importance in the production of the general anæsthetic state. They further add to the growing body of evidence suggesting the lemniscal pathways are not immune to the influence of the commonly used general anæsthetics as originally thought. The apparent paradox of significant depression of a region conventionally linked with transmission and primitive perception of pain (the thalamus) by halothane, an agent which is a poor analgesic clinically, has no obvious explanation at this time.

Acknowledgements

The authors wish to acknowledge gratefully, the assistance of Miss Elaine Konik and Mrs Adella Gilman in the preparation of the manuscript and Mr George LeMasters for the photographic work. The halothane (fluothane) used in this study was supplied by Ayerst Laboratories, Inc.

References

[1]GAIN, E. A. and PALETZ, S. G. (1957). Attempt to Correlate the Clinical Signs of Fluothane Anesthesia with Electroencephalographic Levels. *Canad. Anæsth., Soc. J.*, *4*, 289.

[2]STEPHEN, C. R., MARGOLIS, G., FABIAN, L. W. and BOURGEOIS-GAVARDIN, M. (1958). Laboratory Observations with Fluothane. *Anesthesiology*, *19*, 770.

[3]FRENCH, J. D., VERZEANO, M. and MAGOUN, H. W. (1953). Neural Basis of the Anesthetic State. *A.M.A. Arch. Neurol. & Psychiat.*, *69*, 519.

[4]DAVIS, H. S., DILLON, W. H., COLLINS, W. F. and RANDT, C. T. (1958). The Effect of Anesthetic Agents on Evoked Central Nervous System Responses: Muscle Relaxants and Volatile Agents. *Anesthesiology*, *19*, 441.

[5]DAVIS, H. S., COLLINS, W. F., RANDT, C. T. and DILLON, W. H. (1957). The Effect of Anesthetic Agents on Evoked Central Nervous System Responses: Gaseous Agents. *Anesthesiology*, *18*, 634.

[6]WANG, S. C. and NIMS, L. F. (1948). *J. Pharm. & Exper. Therap.*, *92*, 187.

[7]JASPER, H. H. and AJMONE-MARSAN, C. (1955). Steriotaxic Atlas of Diencephalon of Cat, National Research Council of Canada, Ottawa.

[8]MARSHALL, W. H. (1940). Application of Frozen Sectioning Technic for Cutting Serial Sections Thru Brain. *Stain Technol.*, *15*, 133.

[9]MACINTOSH, R. R. and MUSHIN, W. W. (1946). Physics for the Anæsthetist, Ed. 1, Springfield, Illinois, C. C. Thomas, pp. 5–8.

[10]ZAUDER, K. L. and ORKIN, L. R. (1959). Chamber for Anesthetization of Small Animals. *Anesthesiology*, *20*, 707.

[11]HAUGEN, F. P. and MELZACK, R. (1957). The Effects of Nitrous Oxide on Responses Evoked in the Brain Stem by Tooth Stimulation. *Anesthesiology*, *18*, 183.

[12]MARSHALL, W. H. (1941). Observations on Subcortical Somatic Sensory Mechanisms of Cats under Nembutal Anesthesia. *J. Neurophysiol.*, *4*, 25.

[13]JARCHO, L. W. (1949). Excitability of Cortical Afferent Systems During Barbiturate Anesthesia. *J. Neurophysiol.*, *12*, 447.

[14]KING, E. E., NAQUET, R. and MAGOUN, H. W. (1957). Alterations in Somatic Afferent Transmission Through the Thalamus by Central Mechanisms and Barbiturates. *J. Pharm. & Exper. Therap.*, *119*, 48.

[15]KITAHATA, M. (1949). An Electrophysiological Study on the Sensory Blocking Mechanisms of Inhalation Anesthetics: Nitrous Oxide, Ether and Cyclopropane. Wakayema Medical Reports, *5*, 47.

Thiopentone and methohexital

A comparison as main anæsthetic agents for a standard operation

JOHN W. DUNDEE, MD, PhD, FFARCS

JAMES MOORE, MB, BCh, FFARCS

Department of Anæsthetics, The Queen's University of Belfast, Northern Ireland

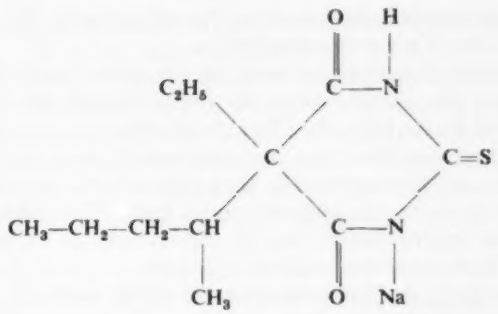
The search for an intravenous anæsthetic, with a more rapid recovery than thiopentone, is still continuing and interest in this field has been re-awakened by recent reports on the use of methohexital (Lilly 25398)[1-4]. The structural formulæ of this drug and thiopentone are shown in FIG. 1.

Methohexital has been undergoing an extensive clinical trial by the authors and their colleagues during the past four years. This preliminary report deals with a comparison of the actions of methohexital and thiopentone in strictly comparable series in which they were used as the main anæsthetic agents. This trial was undertaken to obtain basic data on the complications associated with the use of the new drug and is not intended to include all facets of its action nor to estimate its ultimate place in anæsthesia.

SELECTION OF PATIENTS

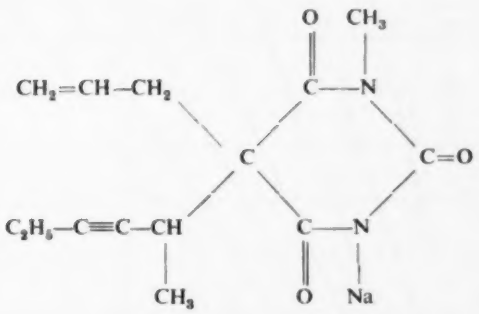
All observations were made in female patients undergoing the operation of curettage with or without preliminary dilatation of the cervix. These patients fulfilled the requirements of Class 1 or 2 physical status according to the classification of the American Society of Anesthesiologists. This excluded 'patients exhibiting severe systemic disturbance which may or may not be associated with a surgical complaint and which seriously interferes with the patient's normal activities'.

One hundred observations were made with each drug and in fifty of these, atropine 0.6mg was used as pre-anæsthetic medication, the remaining fifty receiving 100mg of pethidine in addition to the atropine. In each of these fifty cases one-half had dilatation of the cervix carried



Sodium 5-ethyl-5 (1-methyl-butyl) - thiobarbiturate

THIOPENTONE



Sodium dl - 1 - methyl - 5(allyl) - 5(methyl-2-pentynyl) - barbiturate

METHOHEXITAL

FIG. 1 Formulæ of thiopentone and methohexital

out and in the remaining twenty-five the operation was for the removal of retained products of conception and cervical dilatation was not needed.

ANÆSTHETIC TECHNIQUE

This consisted of induction with a predetermined dose of one or other of the barbiturates and maintenance with nitrous oxide–oxygen (25 per cent oxygen) by the standard Magill circuit, using a total gas flow of 8 l per minute. Anæsthesia was supplemented with additional doses

of barbiturates as required, movement of the patient being the only indication for the use of a supplementary dose.

The standard induction dose was used so that an estimate of the difference between the incremental doses required with each drug could be made and also to allow the effect of premedication on dosage to be studied. The initial dose was given on a weight basis and was based on previous experience with the drug and our estimate of the relative potency of the two compounds under study. The induction dose consisted of approximately 4mg/kg thiopentone or 1.6mg/kg methohexital. Thiopentone was used throughout in a 5 per cent solution and methohexital in a 2 per cent solution and this meant that the volumes of the two solutions used were the same. The diagram shown

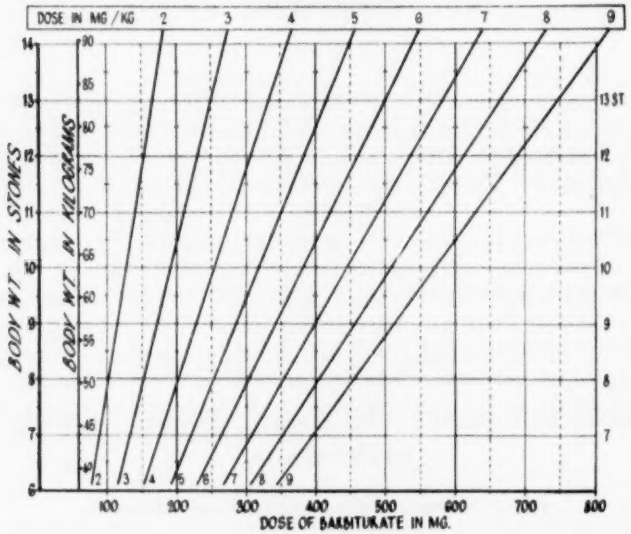


FIG. 2 Graph for rapid calculation of dose in mg/kg

in FIG. 2 was used throughout the study as a quick method of determining the induction dose.

Other drugs were only given when it was not possible safely to provide good operating conditions with the above technique. This happened on occasions when there were gross spontaneous movements of the limbs following the induction of anæsthesia or when there was a marked degree of hypotension with the large dose of barbiturate. The

only supplementary drug used was suxamethonium given in an initial dose of 25mg and repeated if needed.

The nitrous oxide was discontinued immediately the operation was completed and the patient was allowed to breathe a high flow of pure oxygen for exactly one minute. This standardised procedure was adopted so as to allow an assessment of the patient's condition to be made two minutes after the end of the operation (see below). All anæsthetics were administered personally by one or other of the authors.

CLINICAL STUDY OF INDUCTION AGENTS — Form No.

Anaesthetist ... Hospital ... Ward ... Drug ... % ... A.O *

Date ... Operation ... Relaxant / Non-Relaxant *

Patient ... M/F Age ... Wt. ... st. ... lbs. ... kg. Physical Status ...

Pre-anaesthetic medication ... Time ...

Time	I + *	Drug(mg)	N_2O–O_2	B.P.	P.R.	Other Drugs and Comment
Total Dose			mg/kg			

Induction characteristics (circle appropriate items).

Tremor : Spontaneous muscle movements : Coughing : Hiccough : Laryngospasm.

Respiratory Depression : Slight : Marked : No data.

Subjective Signs : Taste in mouth : Pain on injection : Erythematous rash.

Speed of Onset (of Thiopentone) ...

Other comments on Induction :

Induction * Grade 1 2 3

Recovery.

Nausea and Vomiting + —
Thrombosis + —
Other Sequelae.

*To be completed on filling the Record. Any other data to be recorded on back.

FIG. 3 Anæsthetic record form specially designed for clinical study of induction agents

OBSERVATIONS DURING ANÆSTHESIA

A special anæsthetic record card has been designed (FIG. 3) for use during these studies. As can be seen, this chart allows the rapid recording of essential information during short operative procedure and the listing of possible complications during the induction on the chart ensures that their occurrence is more likely to be noted. The presence or absence of the following complications during the induction period were noted as in previous publications[5 6].

(A) *Excitatory phenomena*
These included tremors or spontaneous involuntary muscle movements mostly involving the limbs

(B) *Respiratory upset*
This included coughing, hiccough or laryngospasm following the induction of anæsthesia

(C) *Marked respiratory depression*
This was considered to be present if it was necessary to aid respiration following the induction dose

(D) *Cardiovascular changes*
Systolic blood pressure and pulse rate were recorded before the administration of the premedication, immediately prior to the induction of anæsthesia and at frequent intervals during the anæsthesia. From these data patients were classified in one of the following groups: (1) No hypotension – fall in systolic pressure not exceeding 20mm/Hg. (2) Fall in systolic of between 20 and 40mm/Hg. (3) Fall in systolic pressure exceeding 40mm/Hg. The time taken for the systolic pressure to return within 20 points of the control level was also noted.

Two minutes after conclusion of the operation, all patients were assessed as either (A) awake, (B) safe (presence of corneal, pharyngeal and other protective reflexes) or (C) unsafe (absence of protective reflexes).

All patients were seen on several occasions during the first hour and again six hours after operation. On these occasions, the occurrence of nausea and vomiting or nausea alone was noted. All patients were examined for the presence or absence of venous thrombosis at the site of injection.

GRADES OF ANÆSTHESIA

Each administration was graded according to the scheme previously described by Dundee and Riding[5] and Dundee, Barron and King[6]. The criteria for the different grades are as follows:

Grade 1 No complications during the induction period

Grade 2 The presence of any complication listed above during the induction period, but not of such severity as to make surgery impossible or endanger the life of the patient

Grade 3 The occurrence of severe or dangerous complications

RESULTS

The physical characteristics of the patients and the average duration of anæsthesia and operation in each of the four groups is shown in

Table 1

Details of patients and operations

PRE-ANÆSTHETIC MEDICATION	ATROPINE 0.6mg		PETHIDINE 100mg; ATROPINE 0.6mg	
ANÆSTHESIA	THIOPENTONE	METHOHEXITAL	THIOPENTONE	METHOHEXITAL
Average age (yrs)	31.20 ± 1.29	32.92 ± 1.59	34.28 ± 1.38	32.28 ± 1.27
Average weight (kg)	59.64 ± 1.69	56.20 ± 1.12	61.20 ± 1.18	55.00 ± 1.71
Average duration of anæsthesia (mins)	9.3	10.7	9.7	9.0
Average duration of operation (mins)	8.2	8.7	8.1	7.2

TABLE 1. From this, it can be seen that the two anæsthetic agents were studied in comparable groups of patients having operations of approximately the same duration.

TABLE 2 shows the incidence of complications following the induction of anæsthesia and the condition of the patients at the end of operation. The degree of statistical significance between the incidence of these complications with the two drugs is also shown in this table.

It can be seen that in patients who received atropine only as premedication, the incidence of excitatory phenomena and respiratory upset was significantly greater after methohexital than after thiopentone. However, when pethidine was also given in the premedication, the incidence of these complications was the same for both drugs.

In the atropine series, thiopentone caused a markedly higher incidence of hypotension than the equivalent dose of methohexital. Although the frequency of falls in blood pressure was also greater after thiopentone in the pethidine series, the difference between the two drugs was not significant. After the use of methohexital, blood pressure had always returned to within normal limits in less than ten minutes, whereas, after thiopentone, some degree of hypotension lasted for more than fifteen minutes in 13 per cent of those patients who had a fall in blood pressure.

The smoother induction with thiopentone in those patients premedicated with atropine is shown by a significantly higher number of

Table 2

Incidence of complications during anæsthesia, the grade of induction (*q.v.*) and the condition of the patients two minutes after the end of anæsthesia

	ATROPINE 0.6mg			PETHIDINE 100mg; ATROPINE 0.6mg			TOTAL	
	THIOP	METHOH	DIFFERENCE	THIOP	METHOH	DIFFERENCE	THIOP	METHOH
(A) *Excitatory phenomena*								
Tremor	0	11	$x^2=12.40$ $P<0.001$	1	0	—	1	11
Involuntary limb movements	0	7	—	2	4	—	2	11
Nil	50	33	$x^2=20.48$ $P<0.001$	48	46	nil	98	79
(B) *Respiratory upset*								
Cough/hiccough	3	14	$x^2=8.58$ $P<0.01$	3	4	—	6	18
Laryngospasm	1	3	—	2	2	—	3	5
Nil	47	35	$x^2=9.76$ $P<0.01$	45	44	nil	92	79
(C) *Marked respiratory depression*	1	1	—	0	4	—	1	5
(D) *Hypotension*								
Nil	37	45	$x^2=4.34$ $P<0.05$	39	44	$x^2=1.78$ $P<0.20$	76	89
20–40mm/Hg	11	2	—	7	6	—	18	8
40+mm/Hg	2	3	—	4	0	—	6	3
(E) *Induction grades*								
1	42	28	$x^2=9.34$ $P<0.01$	37	38	nil	79	66
2	7	18	—	11	12	—	18	30
3	1	4	—	2	0	—	3	4
(F) *Condition at end*								
Awake	34	37	nil	13	35	$x^2=19.39$ $P<0.01$	47	72
Safe	15	12	—	32	13	—	47	25
Unsafe	1	1	—	5	2	—	6	3

patients in Grade 1 as compared with methohexital. This difference was not observed in those premedicated with pethidine.

In patients who received atropine as sole premedicant, the number of patients awake at the end of operation was similar for both groups. However, this did not apply when pethidine was given as premedication. Here, a very marked difference was detected between the two drugs and a significantly smaller number were awake after thiopentone than after methohexital. Comparing the effect of the same anæsthetic with the two premedications, it can be seen that the pre-anæsthetic use of pethidine markedly reduced the number of patients who were awake at the end of operation when thiopentone was used, but had no effect when methohexital was employed.

No great importance is attached to the combined totals with different premedicants shown in TABLE 2. These data are included to indicate what results might be expected when methohexital is used routinely with varying types of pre-anæsthetic medication. However, it is of interest to record that the total incidence of hypotension is significantly less with methohexital than with thiopentone ($x^2=5.794$; $P<0.02$) and that a greater number of patients were awake within two minutes of the end of operation after the use of the former drug ($x^2=12.968$; $P<0.001$).

The average dosage of anæsthetics used in the various series is

Table 3

Details of dosage of barbiturates used

PREMEDICATION	ATROPINE 0.6mg		PETHIDINE 100mg; ATROPINE 0.6mg	
ANÆSTHETIC	THIOPENTONE	METHOHEXITAL	THIOPENTONE	METHOHEXITAL
Average induction dose (mg/kg)	3.83 ± 0.05	1.63 ± 0.03	4.09 ± 0.06	1.68 ± 0.04
Average total dose (mg/kg)	4.87 ± 0.18	2.43 ± 0.12	5.21 ± 0.24	2.22 ± 0.09
Incidence of need for supplementary dosage	62 per cent	80 per cent	72 per cent	72 per cent
Ratio of total to induction dose	1.27 ± 0.036	1.49 ± 0.068	1.27 ± 0.058	1.32 ± 0.072

shown in TABLE 3. Because of different potencies it is not possible to compare these doses directly, but although in the atropine series, the ratio of total to induction dose is significantly greater with methohexital than with thiopentone, this difference does not reach the 5 per cent levels of significance. In the pethidine series, there was a negligible difference between this ratio with the two drugs. However, in those patients who received atropine only, the incidence of patients requiring a supplementary dose was significantly greater ($x^2=3.95$; $P<0.05$) with methohexital than with thiopentone. This difference was not detected when pethidine was used as premedication.

SEQUELÆ

This paper is not a detailed study of post-operative vomiting and thus data from all patients were pooled, irrespective of whether they had a dilatation of cervix, which may increase the incidence[7]. This may be justified on the grounds that this procedure was carried out on exactly half the patients in each series. The incidence of nausea and vomiting within the first six hours of the end of anæsthesia is reported in

Table 4

Incidence of sequelæ

	ATROPINE		PETHIDINE AND ATROPINE	
PREMEDICATION	THIOPENTONE	METHOHEXITAL	THIOPENTONE	METHOHEXITAL
First post-op. hour				
Nausea & vomiting	9	6	12	12
Nausea alone	2	5	2	10
1–6 hours after op.				
Nausea & vomiting	8	6	9	10
Nausea alone	1	3	3	11
First six hours after operation				
Nausea & vomiting	13	10	13	15
Nausea alone	2	7	4	13
Nil	35	33	33	22
Venous thrombosis	4	1	2	4

TABLE 4. This was similar with both drugs when atropine alone was given as premedication, but when pethidine was used there was a much higher incidence with methohexital and a significantly smaller number of patients anæsthetised with thiopentone had neither nausea or vomiting during the first six hours after operation ($x^2=4.889$; $P<0.05$). This may be associated with the greater number of patients given methohexital who were ambulant during this period.

The number of cases is much too small to draw any conclusions as to the relative effects of thiopentone and methohexital in causing venous thrombosis. Doses of 30 and 50mg of 2 per cent methohexital were accidentally injected extravenously and there were no sequelæ or complaints of pain despite the absence of any form of treatment.

DISCUSSION

Factual data such as reported in this paper may give a misleading impression of the action of a drug because of the necessary rigidity in classification. This applies to the incidence of excitatory side effects encountered with methohexital since in many instances, these were of a minor nature and did not markedly interfere with the course of anæsthesia. Their severity was usually much less than those encountered following the use of another methylated barbiturate (sodium 1-methyl, 5-ethyl-5′ (1-methyl-propyl)-thiobarbiturate)[6], but they were generally more marked than those associated with the use of hexobarbitone.

Another feature of the use of methohexital which is not apparent from the reported data, is the very rapid and complete recovery of consciousness as compared with patients who received thiopentone. The difference was particularly noticeable when a depressant drug (pethidine) was given as pre-anæsthetic medication. A large number of patients who were operated on in the early morning were walking

around the ward before lunch and had their full mid-day meal when methohexital was used, whereas this was never seen in those in whom thiopentone was used. Although the actual times until patients awakened, as judged by their ability to open their eyes on demand, was approximately the same for both drugs, the hangover associated with thiopentone was usually absent after methohexital. This rapid return of consciousness and absence of a 'hangover' is in full agreement with the results of other workers, some of whom have suggested that the drug would be very suitable for outpatient anæsthesia.

It has been reported elsewhere that the pre-anæsthetic use of an opiate reduces the incidence of spontaneous muscle movements following thiopentone[8]. This has also been shown to apply to inactin[5], but with both of these drugs the incidence of these excitatory phenomena is usually very low and a large series of observations will be necessary to demonstrate this effect. This may explain why it has not been observed in the data presented in TABLE 2.

With the methylated compound, B.137, the beneficial effects of opiates were more marked, but with this drug approximately two thirds of all patients who received atropine as sole premedication exhibited either spontaneous muscle movements or tremor[6]. While this incidence is not as great with methohexital, the protection afforded by the opiate premedication is more marked and this would indicate that the pre-anæsthetic use of an opiate is very desirable when methohexital is to be used as the main anæsthetic agent. As mentioned above the use of this form of premedication is not associated with a delay in return of consciousness such as frequently occurs when thiopentone is used.

It is surprising that none of the early publications on the use of methohexital has drawn attention to the high incidence of abnormal muscle movements associated with its use[1 3 9 10], while this complication did not occur at all in the series reported by Wyant and Barr[4]. However, when Wyant and Chang[2] used the drug as sole anæsthetic (without nitrous oxide and oxygen) for dilatation and curettage, they reported a 35 per cent incidence of minor muscle movements. These conflicting reports stress the importance of the influence of the opiates on clinical data[11], particularly when intravenous anæsthetics are being studied[5].

Our incidence of coughing and hiccough with methohexital, while significantly higher than that following thiopentone, has not been so great as to be considered a major drawback associated with the new drug. This complication is also reduced by the pre-operative use of pethidine ($x^2=6.764$; $P<0.01$).

We have not encountered the high incidence of pain on injection reported by Taylor and Stoelting[3], following the use of a 1 per cent

solution. However, we cannot confirm their finding that venous thrombosis does not occur after its use, although the experience following its accidental extravenous injection suggests that its deleterious effects may be less than those of thiopentone.

It is not proposed in this publication to make any suggestions as to the ultimate place of methohexital in anæsthesia. It would not appear to be an agent suitable for routine use such as thiopentone. While the rapidity of recovery following therapeutic doses seems to be a real advantage, its sparing effect on blood pressure, as compared with thiopentone, is worthy of further study and this may prove even more advantageous than its brevity of action.

SUMMARY

Using a standard anæsthetic technique of barbiturate-nitrous oxide–oxygen for a standard operation, a comparison has been made between thiopentone and methohexital. Equal numbers of cases have been anæsthetised with each drug following premedication with atropine alone and with atropine and pethidine.

In those patients receiving atropine as premedication there was a higher incidence of abnormal muscle movements and respiratory upset (coughing and hiccough) following methohexital than following thiopentone. This was not observed when pethidine was used as premedication. Methohexital caused an appreciably lower incidence of hypotension than an equivalent dose of thiopentone.

One indisputable feature of methohexital was the very rapid recovery and absence of hangover following its use.

Acknowledgements

We are indebted to Mr E. A. G. Cook of Eli Lilly & Co Ltd for generous supplies of methohexital and to Mr G. A. E. Smith for preparing FIGURE 2. Our thanks are also due to Mr H. I. McClure and the staff of Musgrave Park Hospital for providing the facilities for this study.

References

[1] STOELTING, V. K. (1957). *Curr. res. Anesth.*, *36*, 49.
[2] WYANT, G. M. and CHANG, C. A. (1959). *Canad. Anæs. Soc. J.*, *6*, 40.
[3] TAYLOR, C. and STOELTING, V. K. (1960). *Anesthesiology*, *21*, 29.
[4] WYANT, G. M. and BARR, J. S. (1960). *Canad. Anæs. Soc. J.*, *7*, 127.
[5] DUNDEE, J. W. and RIDING, J. E. (1960). *Brit. J. Anæsth.*, *32*, 206.
[6] DUNDEE, J. W., BARRON, D. W. and KING, R. (1960). *Brit. J. Anæsth.*, *32*, 566.
[7] RIDING, J. E. (1960). Personal communication.
[8] DUNDEE, J. W. (1956). Thiopentone and other thiobarbiturates. Edinburgh, Livingstone.
[9] WEYL, R., UNAL, B. and ALPER, Y. (1958). *Surg. Gynæc. and Obstet.*, *107*, 588.
[10] REDISH, C. H., VORE, R. E., CHERNISH, S. M. and GRUBER, C. M. JR (1958). Oral Surgery, *11*, 603.
[11] Editorial (1956). *Anesthesiology*, *17*, 616.

Promethazine

Its influence on the course of thiopentone and methohexital anaesthesia

JAMES MOORE, MB, FFARCS

JOHN W. DUNDEE, MD, PhD, FFARCS, FFARCSI

Department of Anæsthetics, The Queen's University of Belfast, Northern Ireland

A recent publication on the administration of drugs before anæsthesia[1], lists the aims of premedication in the following priority:

1 To prevent undesirable side effects of the anæsthetic
2 To facilitate the induction and maintenance of anæsthesia
3 To prevent undesirable autonomic reflex responses
4 To lessen pre-operative anxiety, fear and emotional tension.

In the past, attention has been almost entirely devoted to the last requirement and the sedative analgesics (and to a lesser extent the barbiturates), have been the drugs of choice in adults. Therapeutic doses of the opiates can cause postural hypotension[2 3 4] and increase the incidence of post-operative nausea and vomiting[5]. Their pre-anæsthetic use facilitates the induction of anæsthesia and reduces the incidence of muscle movement associated with the intravenous barbiturates[6 7 8] and clinical impressions suggest that they reduce the requirements of anæsthetic agents.

The introduction of the phenothiazine drugs has opened up a new field in premedication and they are either used alone or with an analgesic. Promethazine hydrochloride (phenergan) is probably the most popular of these and has been extensively employed for several years[9-17]. The desirable properties claimed for promethazine include its sedative effect[9 16] potentiation of anæsthetic agents[9 11 12 14 16 17] suppression of undesirable reflex activity[10 11 13], anti-sialogogue

action[10 15] and its powerful emetic action[12 13 31]. The marketing of the pamergan preparation containing promethazine and pethidine is indicative of its widespread use.

PRESENT STUDY

This paper reports the findings of a study designed to investigate the effects of the pre-anæsthetic use of promethazine on the course of anæsthesia with two intravenous anæsthetics, thiopentone and methohexital (Lilly 25398). Attention was particularly directed to the above-mentioned requirements of premedication and to examine some of the claims made for promethazine. Methohexital was included in the study because our previous experience showed that its use, in patients premedicated with atropine alone, was associated with a fairly high incidence of complications which were markedly reduced by pethidine premedication[18]. Furthermore, its brevity of action necessitated the frequent use of supplementary doses, so that the potentiating action of promethazine could be studied.

Four forms of premedication were used, half of which contained promethazine 50mg. Except in the early cases these were given at random by the 'double blind' method. The premedicants employed were as follows:

Atropine 0.6mg (A)

Promethazine 50mg, atropine 0.6mg (M)

Pethidine 100mg, atropine 0.6mg (P)

Pethidine 100mg, promethazine 50mg, atropine 0.6mg: pamergan P.100 (PM)

Full doses of these, as contained in the commercially prepared ampoules were always used. When possible, premedication was given forty-five to seventy-five minutes before induction of anæsthesia. A detailed study of the action of these drugs prior to induction of anæsthesia will be published later.

METHOD OF STUDY

This is similar to that described in a previous paper[18] and only brief details will be given here.

Selection of patients

Patients were all of class 1 or 2 physical status (ASA classification) and undergoing uterine curettage with or without dilatation of the cervix. It will be seen from TABLE 1 that random selection has resulted in groups of similar age and weight and there is no marked difference between the average duration of the operation or the anæsthetic in the different series.

Table 1

Physical characteristics of patients, nature and duration of operations

BARBITURATE	THIOPENTONE				METHOHEXITAL			
PRE-ANÆSTHETIC MEDICATION	A	M	P	PM	A	M	P	PM
No of patients	50	36	50	32	59	37	53	34
Average age (yrs)	31.20 ±1.29	32.03 ±2.59	34.28 ±1.38	31.72 ±1.85	32.19 ±1.40	30.97 ±1.36	32.04 ±1.22	34.15 ±1.71
Average weight (kg)	59.64 ±1.69	57.56 ±1.94	61.20 ±1.18	57.34 ±1.99	56.61 ±1.17	56.35 ±0.52	55.58 ±1.68	57.56 ±1.72
Average duration of anæsthesia (mins)	9.31	9.22	9.70	8.96	10.59	10.05	9.02	9.76
Average duration of operation (mins)	8.24	7.73	8.09	7.11	9.02	8.14	7.15	8.15
Percentage of patients having dilatation of cervix	50	69	50	78	56	73	47	74

A atropine 0.6mg
P pethidine 100mg + atropine 0.6mg
M promethazine 50mg + atropine 0.6mg
PM pethidine 100mg + promethazine 50 mg + atropine 0.6mg

Anæsthetic technique

Induction was with either 4mg/kg of 5 per cent thiopentone or 1.6mg/kg of 2 per cent methohexital, and maintenance with 75 per cent nitrous oxide–oxygen, using Magill's circuit and a total gas flow of 8 l/min. Supplementary doses of barbiturate were given to control movement of the patients and if these were not sufficient (or if the barbiturate caused severe hypotension), suxamethonium was used. Pure oxygen was given for one minute at the end of the operation and the patients' condition assessed one minute later. All anæsthetics were administered by the authors.

Observations

In addition to routine dosage, BP and pulse readings, the presence or absence of various complications was noted as follows:

(A) Excitatory phenomena: tremor, spontaneous involuntary movements of limbs.

(B) Respiratory upset: cough, hiccough, laryngospasm.

(C) Marked respiratory depression: considered to be present if it was necessary to aid respiration following the induction dose.

(D) The condition of the patient two minutes after the end of the operation was assessed as being either awake, safe (presence of protective reflexes) or unsafe (protective reflexes absent).

(E) Sequelæ: all patients were seen on several occasions within the first six hours of the end of anæsthesia and the occurrence of nausea and vomiting was noted.

Grades of anæsthesia

Based on the presence of absence of complications following the induction dose, each administration was graded according to the scheme described previously[7 8 18]. The criteria for the different grades were as follows: (1) No complications during the induction. (2) The occurrence of any complication listed above, but not of such severity as to make surgery impossible or to endanger the life of the patient. (3) The occurrence of severe or dangerous complications.

RESULTS

The percentage incidence of various complications recorded following the induction dose of anæsthetic is given in TABLE 2. This table also

Table 2

Analysis of percentage incidence of complications during induction of anæsthesia, frequency of grades of anæsthesia and the condition of the patients two minutes after the end of the operation

BARBITURATE	THIOPENTONE				METHOHEXITAL			
PRE-ANÆSTHETIC MEDICATION	A	M	P	PM	A	M	P	PM
Excitatory phenomena								
Tremor	0	3	2	0	22	51	0	15
Involuntary limb movements	0	17	4	12	17	62	7	26
Nil	100	83	96	88	66	19	93	65
Respiratory upset								
Cough/hiccough	6	0	6	6	31	38	9	21
Laryngospasm	2	8	4	12	5	3	4	3
Nil	94	92	90	84	68	59	87	76
Marked respiratory depression	2	0	0	3	2	0	8	9
Hypotension								
Nil	74	61	78	66	90	73	87	82
20–40mm Hg	22	22	14	22	3	11	13	9
40+	4	17	8	12	7	16	0	9
*Recovery**— 5 mins	54	64	64	36	67	50	71	50
—10 mins	38	29	18	28	33	30	29	30
—10 mins+	8	7	18	36	0	20	0	20
Grade of anæsthesia								
1	84	56	74	44	53	13	75	50
2	14	41	22	53	39	46	25	32
3	2	3	4	3	8	41	0	18
Condition at end of operation								
Awake	68	41	26	34	73	41	70	31
Safe	30	45	64	22	25	59	25	62
Unsafe	2	14	10	44	2	0	5	7

*Percentage of total cases showing any degree of hypotension

A atropine 0.6mg
P pethidine 100mg + atropine 0.6mg
M promethazine 50mg + atropine 0.6mg
PM pethidine 100mg + promethazine 50mg + atropine 0.6mg

shows the frequency of the various grades of anæsthesia in each series and the condition of the patients two minutes after the end of the operation.

The influence of the pre-anæsthetic administration of promethazine on the incidence of complications following the induction of anæsthesia (except respiratory depression of which the incidence is too low for any reliable evaluation) is examined in TABLES 3 and 4. These show that the incidence of excitatory phenomena is greatly increased when promethazine is used prior to methohexital anæsthesia, but this differ-

Table 3

A comparison of the incidence of side effects observed following induction of anæsthesia in patients premedicated with atropine alone and in those who received promethazine and atropine (unless otherwise stated df = 1)

	THIOPENTONE ANÆSTHESIA	METHOHEXITAL ANÆSTHESIA
Excitatory phenomena	None occurred in atropine series as compared with 17 per cent after promethazine	Both tremor ($x^2 = 8.89$, $P < 0.01$) and muscle movement ($x^2 = 20.66$, $P < 0.001$) occurred more frequently after promethazine
Respiratory upset	No difference between series	Differences between the series not significant ($x^2 = 0.70$; $0.50 > P > 0.30$)
Hypotension	Higher incidence after promethazine, but difference not statistically significant ($x^2 = 3.07$; $0.10 > P > 0.05$). Duration of fall similar in both series	Greater incidence with promethazine ($x^2 = 4.57$; $P < 0.05$). No significant difference between duration of fall in the two series
Grades of anæsthesia	Incidence of Grade 1 significantly lower after promethazine. ($x^2 = 8.56$; $P < 0.01$)	Overall course of anæsthesia markedly worse after promethazine. ($x^2 = 20.71$, df = 2, $P < 0.001$)

Table 4

As for TABLE 3, comparing pethidine and pamergan series (df = 1)

	THIOPENTONE ANÆSTHESIA	METHOHEXITAL ANÆSTHESIA
Excitatory phenomena	No difference between series	Higher incidence of patients with no complications after pethidine. ($x^2 = 10.33$; $P < 0.01$)
Respiratory upset	Difference not statistically significant. ($x^2 = 0.60$, $0.50 > P > 0.30$)	Difference not statistically significant. ($x^2 = 1.55$, $0.30 > P > 0.20$)
Hypotension	Greater incidence with pamergan, but difference not significant. ($x^2 = 1.53$, $0.30 > P > 0.20$). Duration of fall similar in both series	No difference in incidence or duration of hypotension
Grades of anæsthesia	Higher incidence of Grade 1 with pethidine ($x^2 = 7.86$, $P < 0.01$)	Higher incidence of Grade 1 with pethidine ($x^2 = 7.29$, $P < 0.01$)

ence could not be observed with thiopentone. However, with this anæsthetic, the incidence of cases showing neither tremors nor spontaneous muscle movements is significantly less in the combined atropine alone and pethidine series than in the pooled pethidine alone and pamergan cases ($x^2 = 10.11$; $P < 0.01$). The use of promethazine had no effect on the incidence of either coughing, hiccough or laryngospasm with either anæsthetic.

Promethazine tends to cause a greater incidence of hypotension, but only in one series (methohexital, TABLE 3) is the difference statistically

significant. When all cases receiving promethazine are pooled, as above, the degrees of significance are: thiopentone anæsthesia, $x^2 = 4.35$; $P < 0.05$; methohexital $x^2 = 3.79$; $0.10 > P > 0.05$. The changes are not related to the total doses of the anæsthetics required as they are based on the initial constant doses of the drugs.

The overall deleterious effect of promethazine premedication on the course of anæsthesia with both thiopentone and methohexital is shown in the consistently lower incidence of complete absence of all complications (grade 1) as compared with patients to whom it was not given.

The average initial and total doses of intravenous anæsthetics administered in all series are shown in TABLE 5. These reveal that attempts to keep the induction doses of each drug constant have been successful and that a comparison of total doses required in each series will reflect the effect of the premedication on the requirements of anæsthetic. This table shows that the pre-anæsthetic use of promethazine significantly increases the requirements of both thiopentone

Table 5

Details of average amount of intravenous anæsthetics required in each series

PRE-ANÆSTHETIC MEDICATION	ATROPINE	PRO-METHAZINE	PETHIDINE	PAMERGAN P100
THIOPENTONE anæsthesia				
Induction	3.83±0.05	4.04±0.05	4.09±0.06	4.16±0.16
Total	4.87±0.18	6.05±0.24	5.21±0.24	5.67±0.23
Ratio Total/Induction dose	1.272	1.497	1.274	1.363
Incidence of use of supplementary dosage	62 per cent	92 per cent	72 per cent	75 per cent
Difference between total doses	$t = 3.90$	$P < 0.001$	$t = 1.33$	$0.20 > P > 0.10$
Difference between incidence of use of supplementary doses	$x^2 = 18.62$	$P < 0.001$	—	—
METHOHEXITAL anæsthesia				
Induction	1.63±0.02	1.60±0.02	1.67±0.04	1.61±0.03
Total	2.44±0.11	2.79±0.09	2.24±0.08	2.30±0.11
Ratio Total/Induction dose	1.497	1.741	1.341	1.429
Incidence of use of supplementary dosage	83 per cent	97 per cent	74 per cent	85 per cent
Difference between total doses	$t = 2.50$	$P < 0.02$	—	
Difference between incidence of use of supplementary dose	$x^2 = 5.04$	$P < 0.05$	$x^2 = 3.287$	$0.20 > P > 0.10$

and methohexital. While in TABLE 5 it would appear that thiopentone was more affected in this respect than methohexital, it must be stated that in many instances the gross degree of involuntary muscle movement which occurred with the promethazine–methohexital sequence necessitated the use of suxamethonium and thus reduced the total dose

of barbiturate. Although, on the average, patients premedicated with pamergan required more barbiturate for the standard operation than those given pethidine, the difference was never statistically significant.

The condition of the patients two minutes after the end of surgery (TABLE 2) has not been discussed until the above data on dosage were presented. Because of the greater amounts of drug used in the promethazine series, it is not possible to present this data as evidence for its action in potentiating barbiturate anæsthesia. However, the use of pamergan, although not associated with greatly increased requirements of either anæsthetic, was followed by a marked reduction in the number of awake patients and in the case of thiopentone only, with a great delay in return of the protective pharyngeal and laryngeal reflexes.

Table 6

Percentage incidence of nausea and vomiting in the first six hours after operation

	A	M	P	PM
THIOPENTONE D and C				
Nausea and vomiting	36	4	32	24
Nausea alone	4	4	8	4
Nil	60	92	60	72
METHOHEXITAL D and C				
Nausea and vomiting	18	22	16	24
Nausea alone	9	7	44	8
Nil	73	71	40	68
THIOPENTONE C				
Nausea and vomiting	16	0	20	0
Nausea alone	4	0	8	11
Nil	80	100	72	89
METHOHEXITAL C				
Nausea and vomiting	19	20	39	22
Nausea alone	23	10	7	11
Nil	58	70	54	67

A atropine 0.6mg
P pethidine 100mg+atropine 0.6mg
M promethazine 50mg+atropine 0.6mg
PM pethidine 100mg+promethazine 50mg+atropine 0.6mg
D and C Dilatation and curettage
C Curettage alone

TABLE 6 shows the incidence of nausea and vomiting occurring during the first six hours after operation. Lack of numbers limit any discussion on this table to those sequelæ following the operation of dilatation and curettage (minimum number of twenty-five cases in each series). A significantly greater number of patients in the promethazine–thiopentone series had no post-operative nausea or vomiting than in the control atropine series ($x^2=7.02$, $P<0.01$), but this did not apply when methohexital was used. The more rapid recovery following this latter drug and thus the greater number of patients who were walking around and eating during the first six hours after operation may explain this difference. However, comparing the effects of

pethidine and pamergan, it was only with methohexital anæsthesia that the protective action of promethazine was statistically significant ($x^2=3.94$, $P<0.05$).

The limitations of data on the incidence of post-operative nausea and vomiting based on such small series is fully appreciated, but the evidence presented is in support of the powerful anti-emetic action of promethazine.

DISCUSSION

It is obvious that our findings are markedly at variance with many of the claims made for promethazine. Rather than facilitate the induction of anæsthesia, this drug in the dosage used made the maintenance of a smooth anæsthetic state very difficult. On looking through the literature, one is amazed to find how few publications deal with the effect of promethazine alone and in most instances it is combined with an analgesic. It is necessary, therefore, to discuss each of the controversial findings in our study in some detail.

The outstanding action of promethazine noted in this study was the increase in tremor and involuntary muscle movements as compared with the incidence following premedication with atropine alone. This action is particularly noticeable with methohexital anæsthesia and since this is a comparatively new drug it is understandable that it may not have been detected previously. However, this effect occurs to a lesser extent with thiopentone and it is surprising that it has not been mentioned by other workers. Gardiner[19] has described a case, in which, following premedication with pethidine 50mg and promethazine 50mg, convulsive movements occurred following the administration of thiopentone. His description of 'flexion and extension at the elbow, combined with pronation and supination' is typical of what we have observed and classed as involuntary muscle movement.

The only explanation which we can offer for the high incidence of excitatory phenomena following the pre-anæsthetic use of promethazine is the combination of two drugs which markedly increase senstitivity to pain. The anti-analgesic action of small doses of thiopentone has recently been described by Clutton Brock[20] and Dundee[21] and will be manifest soon after injection of a dose of 4mg/kg. Methohexital has a qualitatively similar action. The authors have carried out studies (to be published) which demonstrate a marked anti-analgesic effect of doses of 50mg of promethazine. This persists for more than two hours after its intramuscular injection. The combination of these two drugs could easily produce a patient who will react violently to the smallest stimuli (such as application of a face mask), and may even have spontaneous muscle movements. Promethazine 50mg also antagonises the analgesic action of pethidine

100mg and this could account for the similarity between the incidence of excitatory phenomena in the atropine and pamergan series. Our data support the finding of Burn[22] who found that the depressant action of promethazine on muscle tone is very small and suggests that it is of no clinical significance following the 50mg dose used for premedication.

Our study has not demonstrated that promethazine has a depressant action on respiratory reflexes as claimed by other workers[13 23]. However, these claims are all based on its ability to facilitate anæsthesia in the bronchitic, and this type of patient was automatically excluded from our studies.

The incidence of hypotension in those cases premedicated with promethazine or pamergan is not related to the large total dose of barbiturate used, as only the effect of the initial dose was noted. Although promethazine produces less severe falls in blood pressure than some other phenothiazines[24-27], it is to be expected that any drug which produces peripheral vasodilation[28 29] will increase the depressant action of the barbiturates on blood pressure.

With the simple anæsthetic technique of a barbiturate-nitrous oxide-oxygen we cannot agree that the pre-anæsthetic use of promethazine 50mg facilitates the induction of anæsthesia. Our data on the grades of anæsthesia (TABLE 2) are diametrically opposed to this view and while it did not increase the incidence of incidents which endanger the life of the patient (grade 3) when thiopentone was used, this occurred in almost half of the methohexital cases. It is for this reason that the number of subjects in the promethazine and pamergan series was not as great as in the atropine and pethidine series, since it was felt that the continued use of the first two drugs as premedication was not justified.

The dosage data in TABLE 5 demonstrate a higher total requirement of both thiopentone and methohexital in patients who were premedicated with promethazine, as compared with the control atropine series. This is contrary to opinions expressed in the literature on the potentiating effect of promethazine on the narcotic action of anæsthetic drugs[9 11 12 14 16 17]. It is necessary, therefore, to examine the evidence for this so-called potentiation.

In the original publication on chlorpromazine by Courvoisier and her colleagues[29], it was stated that promethazine intensified the hypnotic action of hexobarbitone and butobarbitone in mice, guinea pigs and dogs, but was much less active than chlorpromazine in this respect. Burn[22] reported similar results using pentobarbitone anæsthesia in cats and these agreed with the findings of Dundee and Scott[14] who used thiamylal in rats. All the above conclusions were based on a prolongation of total sleeping time when promethazine was used. A

different approach was that of Sadove, Balagot and Reyes[30] who found that, unlike chlorpromazine, promethazine did not increase the depth of anæsthesia produced by three thiobarbiturates (thiopentone, thiamylal and thialbarbitone), as measured by the electroencephalogram.

Most of the reports in man are based on clinical impressions and are complicated by the number of other drugs used[9 11 12]. The work of Blundell and his colleagues[16] and of Haselhunn and Brunson[17] is worthy of special mention in this respect. The latter workers used a mixed premedication of morphine and pethidine and scopolamine, sometimes combined with a barbiturate and promethazine was given at varying times (including during the anæsthetic). The nature of the operations and anæsthetic techniques varied widely and the duration of anæsthesia was not stated. Their findings of a 40–50 per cent reduction in the dose of thiopentone (in mg/kg/min) when promethazine was used are obviously open to question. Blundell and his co-workers[16] gave 100mg promethazine on the night before operation with half their usual dose of narcotic premedication (nature and dose varied) one hour before operation to which they added a further 100mg of promethazine. Without giving any figures to support their evidence they stated that the above combination resulted in a 25–50 per cent reduction in the requirements of thiopentone.

It is obvious from the above that there are no reliable data in man as to the effect of the pre-anæsthetic use of promethazine on the depth and duration of barbiturate narcosis in man. Animal studies only demonstrate a prolonged sleeping time following the use of the two drugs, with no increase in the depth of anæsthesia.

Our increased total dose of barbiturates required for the standard operation following the pre-anæsthetic use of promethazine is almost certainly related to the high incidence of spontaneous muscle movements found in association with this form of premedication. Supplementary doses of anæsthetic were given frequently to control this movement and in the case of thiopentone this always proved successful, but suxamethonium was sometimes needed with methohexital. Movement in response to a surgical stimulus also occurred more frequently and was more marked when promethazine was used and this further increased the dose of barbiturate required. As suggested previously, this is probably due to the increased sensitivity to somatic pain induced by large doses of promethazine.

The data in TABLE 2 show that promethazine does not markedly prolong the sleeping time after operation with either barbiturate. However, it was noticed frequently that these patients were unusually drowsy during the first two or three hours after anæsthesia. One wonders whether this played any part in the low incidence of nausea

and vomiting found in the patients premedicated with promethazine (TABLE 6).

COMPARISON OF PETHIDINE AND PROMETHAZINE

In view of the widespread use of pethidine and promethazine as pre-anæsthetic medication, it was considered advisable to compare the important effects of these two drugs on the course of anæsthesia, as

Table 7

Comparison of the important findings with pethidine and promethazine on the course and sequelæ of anæsthesia as compared with atropine alone

INDUCTION COMPLICATIONS	PETHIDINE		PROMETHAZINE	
Excitatory phenomena	T	no effect	T	increased incidence
	M	incidence markedly reduced	M	greatly increased incidence
Respiratory upset	T	no effect	T	no effect
	M	incidence reduced	M	no effect
Hypotension	T	no effect	T	incidence increased
	M	no effect	M	incidence increased
Grades of anæsthesia	T	no significant effect	T	lower incidence of Grade 1
	M	higher incidence of Grade 1	M	markedly lowered incidence of Grade 1
Total dosage of barbiturate	T	no effect	T	increased
	M	some reduction	M	increased
Post-operative nausea and vomiting	T	incidence unchanged	T	incidence reduced
	M	incidence increased	M	incidence unaffected

T thiopentone anæsthesia. M methohexital anæsthesia

found in this study (TABLE 7). This shows that, in many respects their actions are directly opposed. We found a lower incidence of pre-operative nausea and dizziness with pamergan P.100 as compared with pethidine alone. There was also a marked reduction in the incidence of restlessness and agitation with pamergan as compared with promethazine. From these points of view the combination has advantages over either drug given separately, but the facilitation of the induction of barbiturate anæsthesia characteristic of the opiates in general is reduced by the addition of promethazine. This disadvantage may be overcome by reducing the dose of promethazine in the mixture. Studies along these lines are at present being carried out.

The data presented in this paper, together with the unpublished results of our pre-anæsthetic studies suggest that, in 50mg doses, promethazine is an unsatisfactory form of pre-anæsthetic medication. Its use before methohexital anæsthesia is particularly dangerous.

SUMMARY AND CONCLUSIONS

A study has been carried out to determine the influence of the pre-anæsthetic use of 50mg promethazine on the course of anæsthesia with thiopentone and methohexital. Observations were all made during or following the operation of uterine curettage and the anæsthetic technique was standard throughout.

Our findings reveal that, under the above conditions, promethazine increased the incidence of muscle movements during anæsthesia and, on the average, it increased the dosage of the barbiturates required for the standard operation. There was a slightly higher incidence of blood pressure falls associated with the use of promethazine.

It is suggested that many of the undesirable actions of promethazine are due to its action in increasing sensitivity to pain.

The actions of promethazine and pethidine as premedicants are directly opposite in many respects.

It is suggested that 50mg promethazine is unsuitable for use as sole premedication.

Acknowledgements

Supplies of promethazine and pamergan P.100 were provided by Dr J. Harper of May and Baker Ltd, to whom we are indebted for co-operation and advice. We are also indebted to Mr E. A. G. Cook of Eli Lilly & Co Ltd, for generous supplies of methohexital. Facilities for this study were provided by Mr H. I. McClure and the staff of the gynæcological department of Musgrave Park Hospital, to whom we are indebted.

References

[1] MUSHIN, W. W. (1960). *Brit. Med. J., 1*, 1558.
[2] DREW, J. H., DRIPPS, R. D. and COMROE, J. H. (1946). *Anesthesiology, 7*, 44.
[3] KING, B. D., ELDER, J. D. JR and DRIPPS, R. D. (1952). *Surg., Gynæc. and Obstet., 94*, 591.
[4] ECKENHOFF, J. E., HELRICH, M. and ROLPH, W. D. JR (1957). *Anesthesiology, 18*, 891.
[5] RIDING, J. E. (1960). *Proc. Roy. Soc. med., 53*, 671.
[6] DUNDEE, J. W. (1956). Thiopentone and other thiobarbiturates, Edinburgh, Livingstone.
[7] DUNDEE, J. W. and RIDING, J. E. (1960). *Brit. J. Anæsth., 32*, 208.
[8] DUNDEE, J. W., BARRON, D. W. and KING, R. (1960). *Brit. J. Anæsth., 32*, 566.
[9] SADOVE, M. S. (1956). *J. Amer. med. Ass., 162*, 712.
[10] BEARD, J. W. (1954). *Proc. Roy. Soc. med., 47*, 407.
[11] WATROUS, W. G. (1957). *Curr. res. Anesth., 36*, 38.
[12] HOPKIN, D. A. B., HURTER, D. and JONES, C. M. (1957). *Anæsthesia, 12*, 276.
[13] DINNICK, O. P. (1954). *Proc. Roy. Soc. med., 47*, 415.
[14] DUNDEE, J. W. and SCOTT, W. E. B. (1958). *Curr. res. Anesth., 37*, 13.
[15] DOBKIN, A. B., WYANT, G. M. and AASHEIM, G. M. (1958). *Anæsthesia, 13*, 63.
[16] BLUNDELL, A. E., PILLION, J. W., BODELL, B. and ANSBRO, F. P. (1959). *Curr. res. Anesth., 38*, 328.

[17]HASELHUNN, D. H. and BRUNSON, E. G. (1959). *Curr. res. Anesth.*, *38*, 485.
[18]DUNDEE, J. W. and MOORE, J. In press.
[19]GARDINER, E. K. (1958). *Brit. med. J.*, *2*, 1227.
[20]CLUTTON-BROCK, J. (1960). *Anæsthesia*, *15*, 71.
[21]DUNDEE, J. W. (1960). *Brit. J. Anæsth.*, *32*, 407.
[22]BURN, J. H. (1954). *Proc. Roy. Soc. med.*, *47*, 617.
[23]FOSTER, C. A. (1960). A practice of anæsthesia by Wylie and Churchill-Davidson, p.707.
[24]MILLER, R. A. (1957). *Canad. Anæs. Soc. J.*, *4*, 364.
[25]ECKENHOFF, J. E., HELRICH, M. and ROLPH, W. D. JR (1957). *Anesthesiology*, *18*, 703.
[26]BEARD, J. W. (1960). General Anæsthesia, Vol. 1. Edited, Evans, F. T. and Gray, T. C., London, Butterworth, 280.
[27]HOWARTH, S. and OWEN, S. G. (1954). *Brit. med. J.*, *2*, 1266.
[28]SHACKMAN, R., WOOD-SMITH, F. G., GRABER, I. G., MELROSE, D. G. and LYNN, R. B. (1954). *Lancet*, *2*, 617.
[29]COURVOISIER, S., FOURNEL, J., DUCROT, R., HOLSKY, M. and KOETSCHET, P. (1953). *Arch. internat. pharmacodyn.*, *92*, 305.
[30]SADOVE, M. S., BALAGOT, R. C. and REYES, R. M. (1956). *Curr. Res. Anæs.*, *35*, 165.
[31]HOWAT, D. D. C. (1960). *Anæsthesia*, *15*, 289.

Phenactropinium chloride

Clinical observations

D. W. EYRE-WALKER, MB, ChB (N.Z.), FFARCS, DA

Lately Anæsthetics Registrar
Chase Farm Hospital, Enfield

This paper records some clinical observations made during controlled hypotension using the drug, phenactropinium chloride (trophenium), in conjunction with ECG and spirometric monitoring. A comprehensive review of the pharmacology of phenactropinium may be found in the paper by Robertson *et al*[1], while details of the spirometry have been described by Atkinson[2].

SELECTION OF PATIENTS

The series comprised fifty-three cases; they were, without exception, female, being gynæcological. The operations performed were Fothergill repairs, sling operations and vaginal hysterectomies.

The selection of these patients has been governed by the fact that at peripheral hospitals little surgery is performed which requires a more than usually bloodless field, except in gynæcology. In this type of case, similar results could be expected with the use of spinal or epidural analgesia, or by the local infiltration of adrenaline; the former technique, however, requires two anæsthetists trained for this procedure if the cases form part of an operation list and there is to be no hold-up between cases; the latter has not found much favour with our surgeons. Controlled hypotension has therefore been our method of choice.

The criteria for the use of hypotensive drugs have been as follows: the absence of a history of previous cardiovascular disease; the absence of a history of previous psychiatric disorders; the absence of a marked degree of symptomless hypertension, *i.e.* above 180mm Hg systolic pressure, or 120mm diastolic; a normal ECG taken, in this series, after induction of anæsthesia but before hypotension; the absence of severe concomitant diseases.

Many of the patients had some degree of mild hypertension and several suffered from chronic respiratory disease. This latter group was

given intense preoperative preparation with breathing exercises, suitable antibiotics and inhalations of isoprenaline – alevaire mixtures combined with postural drainage ; operation was performed when such patients were at their optimal state and none gave cause for anxiety at any stage.

One patient had a history of a detached retina and one had had a nephrectomy, but again neither showed any ill effects.

The average age of the patients was 51, and the range of ages was from 23–73, with the distribution as shown in TABLE 1.

Table 1

AGE GROUP	20–29	30–39	40–49	50–59	60–69	70–79
Repairs	1	4	13	16	4	1
Vag. hysts.	—	—	1	5	4	1
Sling ops.	—	1	1	1	—	—

TECHNIQUE

Premedication was with papaveretum and scopolamine up to the age of 70 and morphine and atropine above this age, given one hour pre-operatively.

More recently, a 'cocktail' has been given in addition, consisting of pethidine 25mg, promethazine 25mg and chlorpromazine 12.5mg, made up to 10ml with water. This 'cocktail' was given slowly intravenously about fifteen minutes before operation, a careful watch being kept on the respiratory rate in particular. Most patients required between 5–10ml. The advantages of combining this with the normal premedication were : the patient arrived in theatre asleep but readily rousable and co-operative ; she required less anæsthetic throughout operation and less post-operative analgesia ; she remained quietly asleep for some time post-operatively without nausea or vomiting, but could be left unwatched safely, as reflexes returned early. This method could lower the blood pressure to about 100mm Hg systolic, at which level no decrease in bleeding is likely, but less hypotensive agent is subsequently required.

Anæsthesia was induced with 5 per cent thiopentone by Mitchell needle in the back of the hand, followed by suxamethonium chloride 25–50mg, oxygenation, a thorough spraying of the larynx and trachea with 4 per cent lignocaine, intubation with a cuffed oral tube and maintenance with nitrous oxide – oxygen in the proportions of five litres to two, by semi-open circuit.

Trichlorethylene was used in the early cases, but was not required when a 'cocktail' was given.

The patient was taken into the operating theatre at this stage and

placed on the table in the lithotomy position. Sphygmomanometer cuff and ECG limb leads were attached to the patient, shoulder rests and elbow rests if the arms tended to hang over the edge of the table, were placed in position and the table tilted 7–10° head-down. Particular care must be taken with positioning the patient, as faulty technique may result in undue pressure on nerve trunks, which in the hypotensive patient especially might give rise to neurological sequelæ.

The blood pressure was recorded and an initial ECG tracing was taken. If this was within normal limits and the surgeon was ready to start, the phenactropinium drip was attached to the Mitchell needle and allowed to run in. Originally the phenactropinium solution was 0.1 per cent strength, as recommended by the manufacturers, but some difficulty in getting satisfactory results at first was overcome by increasing the strength to 0.2 per cent.

Blood pressure readings were taken as often as possible until stable conditions were reached at a suitable level and this was made possible by the anæsthetic technique which gave a steady state of anæsthesia with a spontaneously breathing patient. Thereafter, blood pressure and ECG readings were taken at regular but less frequent intervals.

At the end of the operation, the patients were kept on the table until the blood pressure was over 100mm Hg and were then sent back on tilting trolleys to beds tipped head-down and gradually lowered to the horizontal position as the blood pressure was maintained.

RESULTS

An initial fall in blood pressure was always forthcoming with phenactropinium. Using the weaker solution as mentioned above, the fall was slow and gradual, but even with the stronger solution the rate and degree of fall in blood pressure was unpredictable. In our series the blood pressure of 20 per cent of patients could not be lowered further than a systolic pressure of 90–100mm Hg, however fast the drip was run. The addition of hexamethonium bromide or procaine amide if the pulse was rapid, would not lower the blood pressure further, although subsequent administration of trimetaphan invariably produced a further 10–20mm fall.

Eighty per cent of the series, however, showed a good response initially and of these, 25 per cent showed a precipitate fall to below 60mm. This occurred using both strengths of solution but, naturally, occurred more readily with the stronger. Very few cases with sudden hypotension required anything more active in the way of treatment than stopping the drip. It is of interest and importance that these cases did not necessarily belong to the older age groups in whom an unstable vascular system might be expected.

Tachyphylaxis was seen in 7 per cent of our series, after an initial satisfactory response. The blood pressure could be lowered again by the subsequent administration of either hexamethonium or trimetaphan.

Duration of action

Reports on the drug so far have been in agreement with the makers' claim that, once the administration is stopped, the blood pressure will rise rapidly to normal. This has *not* been our experience. A quick and spontaneous recovery was noted in only 9 per cent of our cases and prolonged periods of post-operative hypotension made us realise the almost universal need for vasopressors to raise the blood pressure to three figures once more. A long-acting vasopressor was required as hypotension may recur once the patient is warded. Methoxamine was found to be the most satisfactory agent for this purpose.

Cardiac effects

ECG tracings of the limb leads were taken before starting the hypotensive agent and abnormal tracings were an indication to refrain from using the technique. During monitoring, where the tracings had been normal previously, cardiac irregularities were seen to develop in a small percentage of cases, and in one or two the irregularity was so closely related to starting and stopping the phenactropinium drip, irrespective of the level of the blood pressure, that it was only reasonable to postulate a direct effect of the drug on the cardiac musculature. Ventricular extrasystoles were the most common and the most serious arrhythmias seen.

Tachycardia may be seen in some cases, but the pulse rate was usually unaffected.

Other ECG changes were inconsistent, but a diminution in voltage and, rarely, depression of the ST segment were observed on occasion.

Respiratory effects

Before this series was begun, it was noticed that respiratory depression was evident in some cases and spirometric monitoring was used throughout this series. Study of the tracings revealed a degree of respiratory depression in almost every case. The reduction in amplitude varied markedly, the range being from 16 per cent to 61 per cent and the mean reduction by 30 per cent of normal. In only one case was there no alteration at all in the amplitude of respiration. The reduction in amplitude was usually associated with an increase in respiratory rate, but minute volumes remained reduced in three-quarters of the cases, the mean reduction being 21 per cent of the pre-hypotensive value. A slight increase of up to 13 per cent in the minute volume was noted in the other 25 per cent of the patients.

Histamine release

A minor point which was investigated was the possibility of histamine release. All patients were given intradermal test doses of phenactropinium and trimetaphan, as well as a control injection of normal saline. Typical wheals and flares were exhibited by all the patients in response to trimetaphan, but no case showed any reaction to either the control or to phenactropinium.

MORBIDITY

One case became mentally confused later in the day of operation, when she got out of bed and threw a jug through a window. The patient was fully recovered by the following morning. This was a case in the early part of the series, before the premedication included a 'cocktail', which might have averted such an occurrence.

A second case developed an ulnar paralysis and legal proceedings were averted only when it was discovered that the patient had had an operation for a cervical rib previously. A more careful assessment preoperatively would have excluded this patient from the series. Recovery was, fortunately, complete.

DISCUSSION

Gillies[3] has postulated that a systolic blood pressure of 60mm Hg is adequate for cellular respiration and metabolism. Furthermore, some degree of ischæmia may be gained by the use of posture, except, as pointed out by Enderby[4], in the perineal region when the legs are raised in the lithotomy position. Posture, then, was of little value in this series, although a slight Trendelenburg tilt was used, and the figure of 60mm Hg systolic pressure remained as an absolute minimum, the pressure being taken at heart level. In point of fact a figure rather above this was aimed at – in the region of 70–75mm Hg – to allow more than adequate oxygenation of heart and brain, without undue fear of brain damage or circulatory collapse. Any condition, such as coughing or straining which would interfere with proper oxygenation, was rigorously avoided.

It was with some dismay, then, that we found respiratory depression to occur in patients undergoing controlled hypotension with phenactropinium. It is difficult to discover how this depression is brought about but, in a recent paper, Deacock and Davies[5] state that they have produced neuromuscular block in animal nerve-muscle preparations with this agent. This block is of the competitive or non-depolarising type and could be reversed with neostigmine. It would seem reasonable to assume that this is the mechanism behind our findings. It would appear to occur irrespective of the level of the blood pressure, but to have some relation to the amount of drug administered.

The blood pressure response varies from patient to patient. Twenty per cent of patients could not be reduced to below 90–100mm Hg; most of these were given other hypotensive agents subsequently. Pure ganglionic blocking agents such as hexamethonium would produce no further fall and it is obvious that full ganglionic paralysis had been achieved. Such cases could be brought to lower levels by the use of trimetaphan and this underlines the point that the latter drug has more than one mode of action; skin testing confirms that histamine is released with trimetaphan but not with phenactropinium. The latter drug is therefore the agent of choice in the allergic type of patient.

Tachyphylaxis, or diminishing response to repeated or prolonged administration of the drug, is encountered with phenactropinium and may lead to more and more rapid administration to maintain results, with consequently greater risk of producing respiratory depression and cardiac irregularities.

Prolongation of action has been noted. The use of the 'cocktail' might be held responsible were it not for the fact that similar results were noted early in the series before the use of these agents. A more important factor is the site of operation; a pelvi-cardiac reflex in vaginal surgery has been postulated to explain post-operative hypotension[6 7].

It would appear that phenactropinium has certain side-effects undesirable in the perfect hypotensive drug.

SUMMARY

A series of fifty-three gynæcological cases is presented, in which the results of phenactropinium-induced hypotension were investigated under ECG and spirometric monitoring.

The drug was found to produce satisfactory operating conditions in most, but not all, cases, but undesirable side-effects were noted and these are commented upon.

Acknowledgements

I would like to express my gratitude to Mr R. M. Millen, whose patients formed this series; and to the anæsthetic staff and in particular to Dr D. Zuck, for their help and advice.

References

[1] ROBERTSON, J. D., GILLIES, J. and SPENCER, K. E. V. (1957). *Brit. J. Anæsth.*, *29*, 342.
[2] ATKINSON, R. S. (1959). *Anæsthesia*, *14*, 231.
[3] GILLIES, J. From the article by Enderby (see reference 4 below).
[4] ENDERBY, G. E. H. (1958). *Brit. med. Bulletin*, *14*, *1*, 49.
[5] DEACOCK, A. R. DE C. and DAVIES, T. D. W. (1958). *Brit. J. Anæsth.*, *30*, 217.
[6] FAIRLEY, H. B. (1956). *Canad. Anæsth. Soc. J.*, *3*, 216.
[7] SNIPER, W. (1960). *Anæsthesia*, *15*, 33.

Pain and the barbiturates

J. CLUTTON-BROCK, MA, MB, BChir, FFARCS, DA

Lecturer in Anæsthetics, University of Bristol

It is usually accepted that the barbiturates do not have analgesic properties, but the writer has often gained the impression, clinically, that sub-anæsthetic doses of thiopentone given intravenously make a patient react more vigorously to a painful stimulus. It seemed, therefore, that it would be of interest to do some pain threshold studies using the barbiturates, particularly thiopentone. The whole subject of the measurement of the pain threshold is well covered in 'Pain' by Wolff and Wolf[1]. In every case measurement of the pain threshold involves the administration of a calibrated painful stimulus to the subject and there are two thresholds that can be measured: one, the threshold for the appreciation of pain; here the stimulus is increased until the subject says that he can just feel pain: and two, the threshold for the response to pain; here the stimulus is increased until there is some physical response on the part of the subject. This response may be muscular movement, elevation of the blood pressure or pulse rate, or the instigation of the psychogalvanic reflex, etc. Perhaps the most accurate method of measuring the thresholds is the radiant heat technique of Hardy, Wolff and Goodel[2]. With this technique, however, there is a considerable danger of burns to the forehead, particularly if the patient is in a state of analgesia. For the pain threshold studies to be described here, a technique has been used which was devised for some experiments in over-ventilation[3]. In the article on this work, only brief mention was made of the technique, so a description of the method will be given here.

METHOD

The apparatus consists of a household spring balance measuring up to 28lb. The pan is removed and replaced by a round-headed screw, the diameter of which is approximately 8mm. The head of this screw is applied with steadily increasing pressure to the anterior surface of the tibia (FIG. 1) in a fresh place for each measurement, until in one

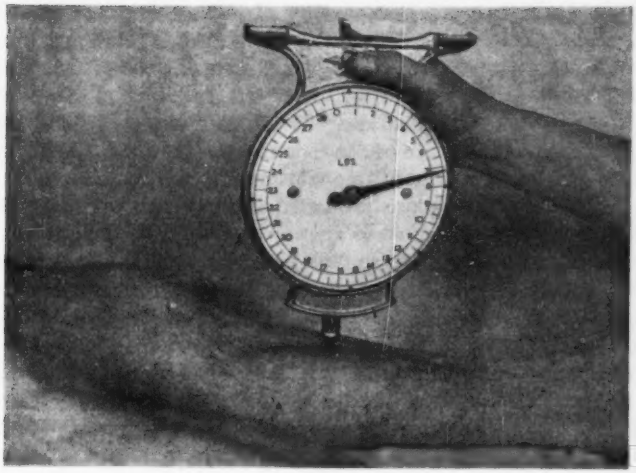


FIG. 1 Method of measuring pain threshold by calibrated pressure from a spring balance

case the subject says that he feels pain and in the other he responds by the withdrawal of the leg or some other obvious movement; at this point, the threshold is read in lbs on the scale. In the first case the subject must, of course, be conscious, but in the second he may be semi-conscious or unconscious. In these studies use has been made of whichever of these measurements was appropriate and, since for this particular investigation the distinction between the two measurements is unimportant, for the sake of simplicity they will both be called the pain threshold.

The tissue damage with this technique is trivial and consists only of a few small bruises on the leg which pass unnoticed by the subject.

This method requires a fair amount of skill and practice to produce consistent results, but it is now found that results, at any one time, are consistent, usually to within one half to one pound. The average of at least two readings is taken.

RESULTS

In order to investigate the effect of the barbiturates on the pain threshold, this has been measured in healthy subjects undergoing routine operative procedures. Readings were taken in the ward before any premedication was given, in the anæsthetic room after the premedication and then after a small dose of a barbiturate intravenously. The premedication has been with various drugs, morphine, papa-

veretum, pethidine, etc. and no very obvious differences have been noticed in the analgesic effects. After a few pilot experiments, a series of twelve experiments was made, using a small dose of thiopentone intravenously as the barbiturate under test. In eleven of these experiments the subject showed an easily detectable rise in the pain threshold after the premedication. In one case no rise was detected. Each of these patients was given a dose of thiopentone somewhere between 25 and 100mg. The actual dose was estimated as one which would make the patient sleepy, but still able to answer questions. This dose was not calculated on a weight basis, but on general considerations according to the age, size and general condition of the patient. In all eleven cases where the pain threshold was raised by the premedication, the small dose of thiopentone reduced the threshold to where it was before the premedication was given. In the one case, when no rise was detected, the thiopentone appeared to have no effect. An experiment was next performed using 100mg of pentobarbitone intravenously. This also removed the analgesic effect of the premedication.

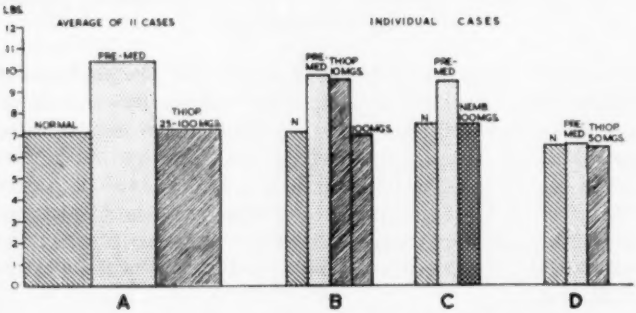


FIG. 2 A Effect of thiopentone on rise in pain threshold produced by preoperative medication. B Effect of inadequate and adequate dose of thiopentone. C Effect of pentobarbitone. D Effect of thiopentone where the premedication has produced no rise in pain threshold.

FIG. 2 illustrates the results of these experiments. At A can be seen, as average readings, the normal pain threshold in the eleven subjects, the effect of the premedication and the effect of a small dose of thiopentone. At B can be seen, in one case, the rise in pain threshold after the premedication, the lack of effect of too small a dose of thiopentone – in this case to 10mg – and the effect of increasing the dose to 100mg. At C can be seen the experiment where pentobarbitone was used and at D the lack of effect of the thiopentone where the premedication caused no significant rise in pain threshold.

Further doses of thiopentone have never shown a rise in the pain threshold while the patient remained conscious. FIG. 3 shows the

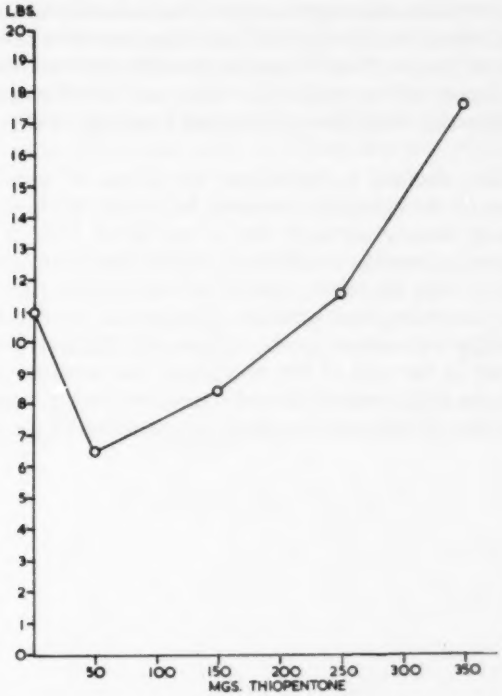


FIG. 3 Effect of thiopentone in increasing doses on the pain threshold

result of an experiment where the threshold for the response to pain was plotted against increasing doses of thiopentone. All these readings were taken within a short time of each other, so that redistribution was minimal. Initially the pain threshold was slightly raised by the drug given for preoperative medication, a small dose of thiopentone caused a fall and this is followed by a rise; but it must be stressed that this rise only occurred after the patient had become unconscious.

The significance of these findings lies, probably, not in the initial effect of any dose of thiopentone – this is transitory – but in the effect of any dose after it has become redistributed. It has been shown by Brodie *et al.*[4], that the plasma level of thiopentone two hours after an

intravenous administration is about one-tenth of the initial concentration. If the initial dose was somewhere between 250 and 500mg, then after two hours, the plasma concentration will be the same as if 25 to 50mg had just been administered. This is the sort of dose that produces a profound antanalgesic effect. The concentration of thiopentone in the plasma after this period only falls extremely slowly, about 10 per cent per hour[5]. Thus the antanalgesic effect of the initial dose of thiopentone may be very prolonged. Also any barbiturates given for premedication may well have a prolonged antanalgesic effect after the operation.

It was then decided to investigate the effects of small doses of thiopentone on the analgesia produced by nitrous oxide and oxygen. Here it soon became obvious that it was more difficult than had been imagined to produce a sufficiently stable state of analgesia for the experiment. It was, therefore, decided to measure the pain threshold of patients recovering from a period of at least an hour of anæsthesia almost entirely with nitrous oxide, oxygen and relaxant. The relaxant was reversed at the end of the operation, and measurements were started as soon as the patient showed signs of returning consciousness. The initial dose of thiopentone given for induction of the anæsthetic

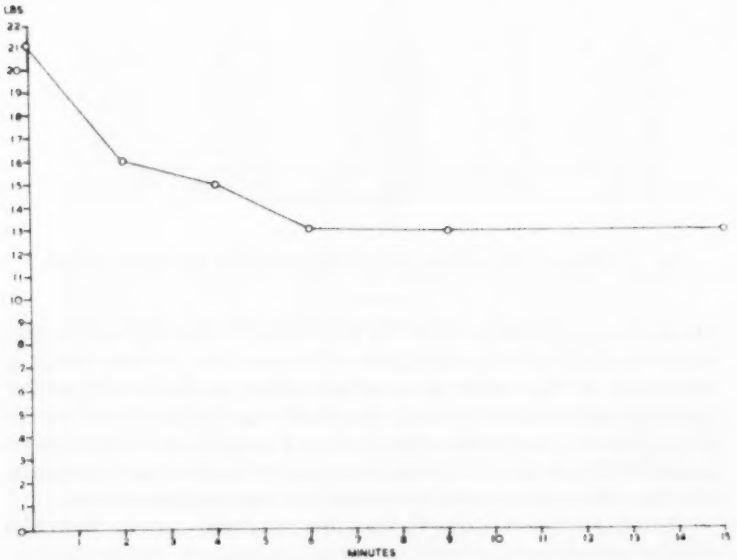


FIG. 4 Rate of fall of pain threshold after anæsthesia with nitrous oxide and oxygen lasting more than one hour

was sufficiently small to be expected to produce no antanalgesia after redistribution. FIG. 4 shows readings of the pain threshold in a patient recovering consciousness after a fairly trivial operation lasting one hour and twenty minutes. It will be seen that the pain threshold starts very high, falls fairly rapidly to begin with and then after about six minutes falls only very slowly. This fits in very well with the expected exponential character of the excretion of nitrous oxide. Three patients, under very similar circumstances, were given small doses of thiopentone during this stage in their recovery. The result of each of these experiments was very similar and FIG. 5 illustrates well what happened.

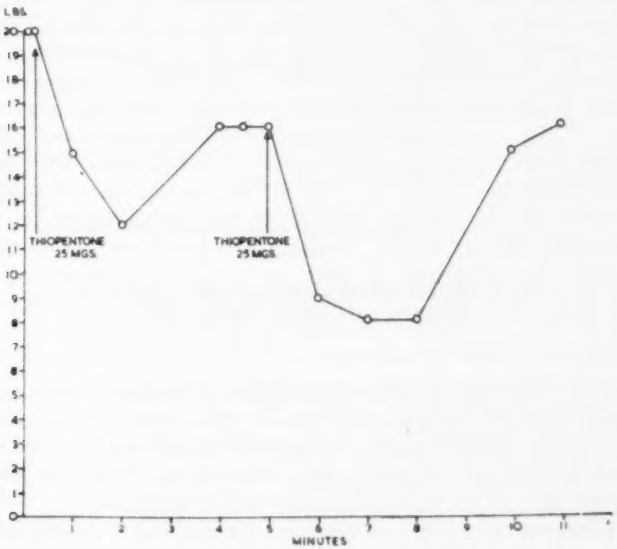


FIG. 5 Effect of thiopentone on the rise in pain threshold produced by nitrous oxide

It will be seen that the pain threshold started at 20 lb, which indicates a state of considerable analgesia, and then fell rapidly after the administration of 25mg of thiopentone. The pain threshold rose again as this became redistributed. When it had reached a more or less steady level, a further dose of thiopentone of 25mg was given and again the pain threshold fell, still further this time and rose again, as might be expected, rather more slowly with the redistribution.

FIG. 6 shows a similar experiment where 100mg of soluble phenobarbitone was given. The antanalgesic effect is very well marked and,

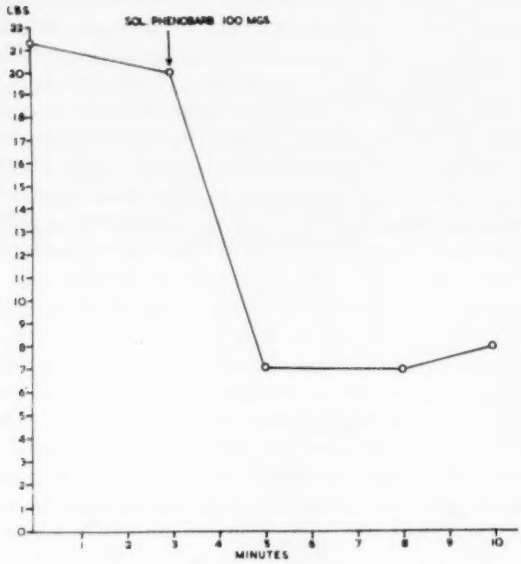


FIG. 6 Effect of soluble phenobarbitone on rise in pain threshold produced by nitrous oxide

of course, there was no rapid redistribution of the phenobarbitone.

These experiments suggest that thiopentone might, paradoxically, in certain doses, actually reduce the depth of anæsthesia from the point of view of response to pain, produced by nitrous oxide and oxygen. That this actually can happen has been shown as follows.

A patient to be anæsthetised only for the removal of a nylon suture, was given a small dose of thiopentone, 100mg, nitrous oxide and oxygen and a sub-relaxant dose of gallamine. After the operation had been proceeding for half-an-hour, he was allowed to come into equilibrium with 50 per cent nitrous oxide and oxygen for ten minutes. The surgeon was then asked to excise a small piece of skin from the edge of the wound. The patient did not move. He was then given 25mg of thiopentone intravenously and the surgeon asked to remove a similiar small piece of skin from the edge of the wound. The patient reacted vigorously. After an interval of five minutes, allowing considerable redistribution of the thiopentone, the excision of a further small piece of skin caused just a slight movement of the head.

The importance of these experiments, like the experiments on the effect of the opiates, lies, not in the immediate effect of any dose of

thiopentone, but on the effect of the thiopentone after redistribution. Here the effect of a dose of, say, 250–500mg of thiopentone for induction may immediately produce anæsthesia; but after redistribution may actually serve to lighten the anæsthesia produced by nitrous oxide and oxygen. Since this strange property of the barbiturates became apparent, the induction dose of thiopentone has been reduced to something between 25 and 150mg, depending on the patient, *i.e.* a dose, which, when redistributed, should not have an antanalgesic effect, but is just sufficient to make the patient accept the face-piece comfortably. These patients seem to be much more comfortable post-operatively and the anæsthesia produced by nitrous oxide and oxygen seems altogether easier and smoother; indeed, it has seemed advisable to reduce the dose of any opiate used pre-operatively, since the patients no longer have so much respiratory stimulus from pain. Hydroxydione has not shown an antanalgesic effect, but seems only to cause a rise in the pain threshold. This may account for the increase in comfort that has been reported after the use of this drug.

The clinical applications of these results are mostly fairly obvious, though some are less so. Barbiturates should not be prescribed the night before operation, nor should they be used for premedication before operations where there is likely to be any significant post-operative pain. If, however, the pain is associated with muscular spasm, then, of course, the barbiturates may relieve this rather than make it worse. A dose of thiopentone for induction should be given which is small enough to have no antanalgesic effect after redistribution. It is not only post-operative comfort that is at stake here; if a patient, through some error in technique, happens to return to consciousness during an operation, if he has had a sufficient dose of barbiturate he will be in pain. If he has not, he may well remain analgesic during the time that he is awake. Small doses of intravenous barbiturates are often given to a patient who is having a regional block. These barbiturates will be useful if the regional block is a good one, but they will be worse than useless if there is any residual pain. Furthermore, when the regional block wears off the patient will be made unnecessarily uncomfortable.

DISCUSSION

Any neurophysiological explanation for these findings must, of necessity, be speculative, but it seems most likely that the explanation will be found in the effects of the barbiturates on the reticular system of the brain stem. Brazier[6] has shown that an early effect of the barbiturates is to lessen the primary responses to a flash of light, as recorded from the cat's cerebral cortex, but to increase considerably the secondary response. It is believed that the pathway for this secondary response

goes through the reticular system. Brazier suggests that at this stage of barbiturate anæsthesia some inhibitory system, possibly in the diffuse ascending system, has itself been inhibited. A deeper level of anæsthesia can, of course, be reached, at which this differential depression is lost.

It is believed that the pathways for pain may be made up very largely of relays through the central reticular formation[7], so it seems not unreasonable to expect that this pathway could be facilitated in exactly the same way as the secondary response described above.

SUMMARY

A new method of measuring the pain thresholds is described. This causes very little tissue damage and appears to give consistent results. It does, however, require a fair amount of practice and skill. It has been shown that the barbiturates, in doses insufficient to cause loss of consciousness, antagonise the analgesic effect of both the opiates and nitrous oxide.

The clinical application of these findings is discussed and a possible neurophysiological explanation is suggested.

References

[1] WOLFF, H. G. and WOLF, S. (1958). Pain. Oxford.
[2] HARDY, J. D., WOLFF, H. G. and GOODEL, H. (1940). *J. Clin. Investigation, 19*, 649.
[3] CLUTTON-BROCK, J. (1957). *Brit. J. Anæsth., 29*, 111.
[4] BRODIE, B. B., MARK, L. C., PAPPER, E. M., LIEF, P. A., BERNSTEIN, E. and ROVENSTINE, E. A. (1950). *J. Pharmacol., 98*, 85.
[5] Ibid.
[6] BRAZIER, M. A. B. (1954). Brain Mechanisms and Consciousness. 163. Oxford.
[7] MAGOUN, H. W. (1958). The Waking Brain. 78. U.S.A.

Decamethonium in clinical anæsthesia

G. C. FISK, MA, BM, FFARCS

Registrar, Department of Anæsthetics
Guy's Hospital

Formerly Anæsthetic Registrar
The Royal North Shore Hospital of Sydney

Decamethonium (C.10) is a muscle relaxant which is not widely used at present as an adjunct to anæsthesia in Great Britain. In fact, one preparation has recently been withdrawn from the market and the removal of the remaining source of supply has been threatened[1]. In some centres, however, decamethonium is found to be a most useful relaxant and enjoys a steady popularity[1 2 3]. Crawshawe[4] (1958) reported to the Australian Society of Anæsthetists that decamethonium was used on 5,921 occasions out of approximately 30,000 anæsthetics at Sydney Hospital. A brief review of the published reports of the use of this drug in anæsthesia and a consideration of its pharmacology, may indicate why it has been abandoned by most, but retained by a few.

The drug is chemically bis trimethyl ammonium decane diiodide or dibromide. It is usually classified as a depolarising muscle relaxant and is available as a 0.2 per cent solution which is readily miscible with thiopentone.

HISTORICAL OUTLINE

In 1948, when the use of curare in anæsthesia was increasing rapidly and a cheaper synthetic substitute was being sought, Barlow and Ing[5] and Paton and Zaimis[6] reported a curare-like action in the polymethylene bis-quaternary ammonium salts. In 1949, Paton and Zaimis[7] suggested that decamethonium had clinical potentialities and Organe, Paton and Zaimis[8] published the results of administration of the drug to human subjects. The first clinical reports also appeared in 1949. The Medical Research Council and the Anæsthetic Section of the Royal Society of Medicine had planned a large formal clinical trial, but the drug appeared on the market before this could be carried out.

Substance of a paper read to the Department of Anæsthetics, Guy's Hospital on the 23rd March 1960

Two small series were immediately published by Organe[9] (50 cases) and Hewer *et al*[10] (85 cases) but the full trial was not completed. In the same year, Holaday, Harvey and Grob[11] published the first series from the United States of 172 cases.

TABLE I shows the chronological incidence of the reports of the use of decamethonium in anæsthesia which I have been able to collect from the literature.

Table 1

YEAR	FAVOURABLE	FAVOURABLE BUT SOME CASES OF PROLONGED ACTION	UNFAVOURABLE
1949	3	–	–
1950	2	2	2
1951	3	1	1
1952	–	–	2
1953	2	1	–
1954	1	–	–
1955	1	–	–
1956	–	1	–
1957	–	–	–
1958	–	1	–
1959	1	–	–

It can be seen that reports of prolonged paralysis began to appear in 1950 and that following these, the incidence of reports of the use of the drug seems to decline.

APPLIED PHARMACOLOGY

Decamethonium causes muscle relaxation by blocking neuromuscular conduction. In animals[12] this block is usually of the depolarisation type, but in monkeys there is an initial depolarisation block followed by a non-depolarisation block which is reversible by neostigmine. In man[13 14] the initial dose causes a depolarisation block, but after repeated doses there is a change to a dual block in which the non-depolarising element lasts longer than the block following the first dose. In myasthenic patients[15] the initial dose causes a dual block. This mechanism explains some important clinical phenomena:

Potentiation of the effect of non-depolarising relaxants when they follow C.10 and antagonism when they precede it

Tachyphylaxis

Prolonged paralysis after repeated doses which is often reversible by neostigmine

A dose of 3–5mg in adults will cause apnœa lasting from ten to twenty minutes. Side effects in clinical dosage are almost non-existent and rare cardiovascular effects which have been reported may be due to other factors[16]. Neither bronchospasm nor the effects of histamine release are seen. An intravenous dose of decamethonium is distributed in the extracellular fluid of the body and largely excreted by the kidneys[12].

ANALYSIS OF CLINICAL REPORTS

TABLES 2, 3 and 4 give details of the reports indicated in columns 1, 2 and 3 respectively of TABLE 1.

Table 2

Entirely favourable clinical reports

AUTHORS		NUMBER OF CASES
Hewer *et al* (1949)[10]		85
Organe (1949)[9]		150
Holaday, Harvey and Grob (1949)[11]		172
Ellerker (1950)[17]		208
Bailey and Murphy (1951)[18]		500
Volpitto (1951)[19]		627
Austin and Mering (1951)[20]		67
Colon-Yordon, Mackrell and Stone (1953)[21]		1,038
Spencer and Coakley (1955)[22]		2,403
Enderby (1959)[1]	more than	4,000
	TOTAL	9,250
In addition		
Roberts (1950)[23]	'Large series of cases'	
Snyder (1953)[24]	'Limited experience'	
Jewell (1954)[25]	No figures	

Table 3

Favourable clinical reports containing some cases of prolonged apnœa

AUTHORS	TOTAL NUMBER OF CASES	PROLONGED APNŒA
Harris and Dripps (1950)[26]	250	4
Hunter (1950)[27]	?	1
Foldes and Mackaj (1951)[28]	204	4
Rizzi and Ricci (1953)[29]	1,109	9
Lawson (1958)[2]	?	2
TOTAL	1,563	20
In addition		
Organe (1956)[3]	'Several thousand'	'A few'

Table 4

Unfavourable clinical reports

AUTHORS	TOTAL NUMBER OF CASES	PROLONGED APNŒA
Vetten and Nicholson (1950)[30]	223	1
Gray (1950)[31]	?	4
Barry, Stratton and Sutherland (1951)[32]	175	2
Guernier and Mason (1952)[16]	233	1 (and 4 abnormal cardiovascular responses)
Ruddell (1952)[33]	?	1
TOTAL	631	9

It will be noted that the numbers of cases are not mentioned in some of the reports. Nevertheless, more than 11,344 cases in which decamethonium has been used have been reported and of these twenty-nine (plus 'a few') have shown prolonged action. Further, the largest series are those which report favourably on its use. Perhaps this may be because unfortunate experiences led to the abandonment of the drug before its limitations and indications were understood. One cannot know the reason with certainty.

TABLE 5 presents a breakdown of the details given of the cases in which a prolonged action occurred.

Where sufficient details have been given of the circumstances which led up to the development of persistent post-operative paralysis, it can be seen that in most cases complications may be attributed to factors which were either avoidable or constituted a contraindication to the use of such a relaxant. Overdosage is the most important of these.

Table 5

	NO.	AGE	SEX	CLINICAL CONDITION	DOSE	DURATION OF RESPIRATORY INSUFFICIENCY	FATE
Harris and Dripps (1950)[26]	1	53	M	Gastrectomy	11mg	1 hour	Recovery
	2–4	*No details*					Recovery
Hunter (1950)[27]	5	Long and difficult gastrectomy Spontaneous, depressed respiration			30mg	10 hours	Recovery
Vetten and Nicholson (1950)[30]	6				Moderate	Severe	?
Gray (1950)[31]	7	46	F	Obese. Trendelenberg Assisted respiration	8mg	4 hours 'Intercostal rather than diaphragmatic breathing'	Recovery
	8		F	Myocardial degeneration Abdomino-perineal resection	4mg	?	Sudden collapse 1 hour after operation – died
	9–10			*No details*			Recovery
Foldes and Mackaj (1951)[28]	11	68	F	Emaciated. Over-premedicated	3mg	40 minutes	Recovery
	12–14			*No details*			Recovery
Barry, Stratton and Sutherland (1951)[32]	15	45	M	Good risk gastrectomy	12mg	Days	Recovery
	16	75	M	Weight loss. Nephrectomy for nephrolithiasis	7mg	?	Recovery
Guernier and Mason (1952)[16]	17	65	M	Chronic bronchitis. Frail	8mg	2 hours	Recovery
Ruddell (1952)[33]	18	58	M	Gastrectomy for ulcer	13mg 6mg neostigmine +250mg suxamethonium	?	Recovery
Rizzi and Ricci (1953)[29]	19–20			Thoracotomy	?	10–60 minutes	Recovery
	20–27			Laparotomy	?		Recovery
Lawson (1958)[2]	28				12.5mg	? neostigmine	Recovery
	29					? neostigmine	Recovery
In addition Organe (1956)[3]	?				More than 10mg	Responded to neostigmine	Recovery

Clinical experience has shown that a total dose of 10mg should not be exceeded for fear of dual block and persistent paralysis[3] and a dose of 5mg should rarely be exceeded. Thus in cases No 1, 5, 15, 18 and 28 dosage may be considered to have been excessive and in cases No 11 and 17 there may have been a relative overdose in poor risk patients. In cases No 7, 8 and 11 other factors may have contributed to the clinical picture.

In all these reports of post-operative difficulty after the use of decamethonium, only one death (case No 8) is mentioned and here it was felt that post-operative respiratory insufficiency was a major factor in the causation of death. With one exception (case No 6), eventual recovery was specifically mentioned in all the other cases.

Guernier and Mason[16] reported four cases of cardiovascular disturbances which they attributed to decamethonium. In one of these there was a paroxysmal tachycardia and in the other three bradycardia and

hypotension occurred. These appear to be isolated incidences and others have found the drug to be remarkably free from untoward circulatory effects.

DISCUSSION

I feel that viewed in this way, the evidence that decamethonium may give rise to untoward difficulties if used as an anæsthetic adjunct is not as convincing as at first it might seem. Personal experience and that of many others[1 2 3 4] would suggest that it is a drug which must be used with care and with an appreciation of its limitations. In particular, overdosage, including relative overdosage, must be avoided. In the earlier days of its use, pentamethonium was suggested[7] and tried[8 9 32] as an antidote to decamethonium, but it was usually ineffective and caused disastrous lowering of blood pressure. There have, however, been several reports of the successful use of neostigmine in reversing a prolonged paralysis due to decamethonium[2 3 33]. In clinical use, the reliability of action of decamethonium makes an antidote unnecessary, but should a prolonged action occur, then it is likely that this may be due to a dual block, and it would be logical to observe the effect of a small dose of an anticurare drug.

The advantages which may be attributed to decamethonium may be listed as:

A reliable action of an initial dose, which will persist for ten to twenty minutes, terminating with a relatively sharp end point

It may be used together with small doses of suxamethonium and may be followed by non-depolarising relaxants

The absence of cardiovascular and other untoward side effects

The solution is miscible with thiopentone

Two cardinal rules are suggested for the safe use of this relaxant:

The drug is contraindicated in all cases where the action of muscle relaxants may be expected to be abnormal, *e.g.* myasthenia, cachexia and electrolyte disturbances.

A total dose of 5mg should rarely be exceeded. Further relaxation may be procured by using small doses of suxamethonium or following with a non-depolarising relaxant.

Used as indicated decamethonium is a most useful drug for reducing reflex responses in surgery of the limbs, or combined with suxamethonium for intubation in surgery of the head and neck, in obstetric anæsthesia and for smooth induction in thoracic surgery. My personal experience of the drug does not include any cases of post-operative paralysis, although these have occurred with other muscle relaxants.

SUMMARY

The history of the introduction of decamethonium into clinical anæs-

thesia, and subsequent reports of its use are reviewed. The applied pharmacology of the drug is outlined. Published reports of the use of the drug are analysed and the details of cases in which persistent post-operative paralysis occurred are considered. It is suggested that decamethonium is a useful and safe relaxant in clinical anæsthesia when due regard is paid to its limitations and contraindications.

Acknowledgement

I should like to acknowledge the encouragement and advice given me by Dr P. J. Helliwell, Director of the Department of Anæsthetics, Guy's Hospital.

References

[1] ENDERBY, G. E. H. (1959). *Anæsthesia, 14*, 138.
[2] LAWSON, J. I. M. (1958). *Brit. J. Anæsth., 30*, 240.
[3] ORGANE, G. (1956). *Canad. Anæs. Soc. J., 3*, 5.
[4] CRAWSHAWE, B. (1960). Personal communication.
[5] BARLOW, R. B. and ING, H. R. (1948). *Nature, 161*, 718.
[6] PATON, W. D. M. and ZAIMIS, E. J. (1948). *Nature, 161*, 718.
[7] PATON, W. D. M. and ZAIMIS, E. J. (1949). *Nature, 162*, 810.
[8] ORGANE, G., PATON, W. D. M. and ZAIMIS, E. J. (1949). *Lancet, 1*, 21.
[9] ORGANE, G. (1949). *Lancet, 1*, 773.
[10] HEWER, A. J. H., LUCAS, B. G. B., PRESCOTT, F. and ROWBOTHAM, E. S. (1949). *Lancet, 1*, 816.
[11] HOLADAY, D. A., HARVEY, A. M. and GROB, D. (1949). *New England J. Med., 241*, 817.
[12] PATON, W. D. M. and ZAIMIS, E. J. (1952). *Pharmacol. Rev., 4*, 219.
[13] FOLDES, F. F., WNUCK, B. S., HODGES, R. J. H., THESLEFF, S. and DE BEER, E. J. (1957). *Anesth. and Anal., 36*, 23.
[14] CHURCHILL-DAVIDSON, H. C. and CHRISTIE, T. H. (1959). *Brit. J. Anæsth., 31*, 290.
[15] CHURCHILL-DAVIDSON, H. C. and RICHARDSON, A. T. (1953). *J. Physiol., 122*, 252.
[16] GUERNIER, S. M. and MASON, J. C. (1952). *Brit. Med. J., 1*, 1329.
[17] ELLERKER, A. R. (1950). *Brit. Med. J., 2*, 398.
[18] BAILEY, P. J. and MURPHY, F. J. (1951). *Anesthesiology, 12*, 63.
[19] VOLPITTO, P. P. (1951). *Anesthesiology, 12*, 648.
[20] AUSTIN, B. R. and MERING, T. W. (1951). *Amer. J. Obstet. Gynec., 62*, 143.
[21] COLON-YORDAN, E., MACKRELL, T. M. and STONE, H. H. (1953). *Anesthesiology, 14*, 255.
[22] SPENCER, C. H. and COAKLEY, C. S. (1955). *Anesthesiology, 16*, 125.
[23] ROBERTS, T. B. L. (1950). *Lancet, 1*, 373.
[24] SNYDER, J. J. (1953). *U.S. Armed Forces Med. J., IV*, 1037.
[25] JEWELL, T. C. (1954), *Amer. J. Obstet. Gynec., 67*, 273.
[26] HARRIS, L. C. and DRIPPS, R. D. (1950). *Anesthesiology, 11*, 215.
[27] HUNTER, A. R. (1950). *Brit. J. Anæsth., 22*, 218.
[28] FOLDES, F. F. and MACKAJ, R. S. (1951). *Anesthesiology, 12*, 366.
[29] RIZZI, R. and RICCI, C. (1953). *Anesth. and Anal., 32*, 400.
[30] VETTEN, K. B. and NICHOLSON, J. C. (1950). *Anæsthesia, 5*, 175.
[31] GRAY, A. J. (1950). *Lancet, 1*, 253.
[32] BARRY, C. T., STRATTON, J. and SUTHERLAND, A. R. (1951). *Lancet, 1*, 507.
[33] RUDDELL, J. S. (1952). *Lancet, 2*, 341.

SUMMARIES OF PAPERS

PRESENTED AT THE ANNUAL GENERAL MEETING OF THE

ASSOCIATION OF ANÆSTHETISTS

OF GREAT BRITAIN AND IRELAND

FRIDAY 4 NOVEMBER 1960

The myth of phenothiazine potentiation

JOHN W. DUNDEE

JAMES MOORE

BELFAST

When investigating a method of analgesimetry, the authors found a mixture of promethazine and pethidine (pamergan P.100) to be devoid of analgesic activity. Subsequent studies showed promethazine to have a marked anti-analgesic action and to antagonise pethidine-induced analgesia. Contrary to accepted views, we were only able to detect analgesic activity with three (chlorpromazine, promazine and trimeprazine) of the nine phenothiazines studied.

The effect of phenothiazine premedication on the dose of methohexital required to maintain anæsthesia for surface operations was studied. Only the drugs which showed analgesic activity reduced the average requirements to a significant degree. On the other hand, pethidine markedly decreased barbiturate requirements.

Despite the claims that the phenothiazines 'facilitate the course of anæsthesia', the authors found that none of them beneficially affected the course of methohexital anæsthesia. Markedly anti-analgesic members (promethazine and mepazine) increased the incidence of abnormal muscle movements and respiratory upset, following injection of this barbiturate, and increased average drug requirements for a standard

operation. Even with small doses of promethazine these effects were observed, although to a lesser degree.

Our studies do not shown any 'potentiating' action of the phenothiazines in general and their ability, in this respect, appears to be related to their analgesic activity. Promethazine, in particular, has adverse effects on all the various facets of barbiturate narcosis. Observations after its use with large doses of pethidine or other analgesics, and erroneously attributing reductions in barbiturate dosage and side effects during anæsthesia to the promethazine, seem to be the origin of the myth of phenothiazine potentiation.

The Cardiff calculator for halothane in the closed circuit

S. GALLOON, CARDIFF

Economy is the only reason for the use of small gas flows in the closed circuit. Halothane is expensive and small gas flows would seem desirable; it is preferable to use it with small flows, but since the introduction of this agent, argument has waxed and waned over the safety, or otherwise, of using such a potent anæsthetic in this way. There is no doubt that a knowledge of the concentration of vapour inspired by the patient would make this method safer.

In a series of articles recently published from the Department of Anæsthetics in Cardiff, the factors influencing the concentration of vapour inspired were shown to be the 'vapour concentration' (tap setting), the fresh-gas flow, the ventilation of the patient and the uptake of halothane and oxygen by the patient. It was also shown that theoretical calculations of the inspired vapour concentration in various circumstances are very close to the actual concentrations measured in the operating theatre.

A calculator, based on these theoretical calculations, can easily be designed to provide the anæsthetist with a reasonably close estimate of the inspired concentration of halothane, if he knows the 'vaporizer concentration', the fresh-gas flow and the ventilation. Most of the vaporizers in use in the VOC (vaporizer outside the breathing circuit) are calibrated and a calculator for the VOC is demonstrated and its use explained. The figures shown on the calculator were compared with the measured concentration of halothane inspired by a number of patients in the operating theatre; the agreement between the two sets

of figures illustrates the value of such a calculator in clinical anæsthesia. A similar calculator can be made for the VIC (vaporizer inside the breathing circuit), but would be of little use at present, as most of the vaporizers used inside the breathing circuit are not calibrated. A method of calibration is suggested and an example shown.

The figures given by the calculator are based on the assumption that the oxygen uptake is 200ml/min and the halothane uptake 15ml/min for each per cent alveolar concentration, an average figure taken from a number of measurements of halothane uptake made in this department during clinical anæsthesia and yet to be published. Graphs are shown which demonstrate that individual variations in the uptake of oxygen and halothane only alter the inspired concentrations on the calculator by up to 20 per cent.

Respiratory insufficiency following anaesthesia for aortic embolectomy

J. I. MURRAY LAWSON

R. D. M. DAVIE

DUNDEE

Two consecutive cases of persistent respiratory insufficiency following d'tubocurarine, thiopentone, nitrous oxide and oxygen anæsthesia for the operation of aortic embolectomy are described. Both patients suffered from serious ischæmic heart and peripheral vascular disease.

The pattern of their post-operative respiratory insufficiency differed from the more generally recognised picture of 'neostigmine-resistant curarisation', first written about by Hunter (1956) and Foster (1956), in that they recovered full consciousness and were able to move and to open their eyes before the return of adequate respiration. They were, in fact, suffering from a specific intercostal paralysis.

The importance of muscle blood flow in influencing the duration of neuromuscular block has been emphasised by Churchill-Davidson and Richardson (1952) and by Wylie and Churchill-Davidson (1960). We suggest that in our two patients the persistent intercostal paralysis was due to an intercostal ischæmia resulting from severe atheromatous changes in the aorta. In this condition the pathology is usually most

marked at the orifices of branches, especially those of the intercostal arteries. When the atheroma is severe, as it tends to be in the type of patient described, the orifices of these arteries become seriously narrowed. This impedes the blood supply of the intercostal muscles and is a reasonable explanation for the occasional occurrence of paralysis in these cases. This ischæmia will be aggravated by the slightest degree of deterioration of the circulation.

Treatment consists of adequate, but not excessive neostigmine, effective ventilation and support of the circulation for as long as is necessary. Patience is most important and polypharmacy must be avoided.

As the patients are distressed, and as there is no question of the ætiology being central depression, sedation is indicated, *e.g.*, pethidine intravenously. This helps to break the vicious circle of restlessness, respiratory insufficiency and asphyxia. The patients' distress is relieved, and, by reducing their respiratory requirements to a level nearer their capacity, their management until recovery of the intercostals is made easier.

References

HUNTER, A. R. (1956). *Brit. Med. J.*, *2*, 919.
FOSTER, P. A. (1956). *Brit. J. Anæsth.*, *28*, 488.
CHURCHILL-DAVIDSON, H. C. and RICHARDSON, A. T. (1952). *Proc. Roy. Soc. med.*, *45*, 179.
WYLIE, W. D. and CHURCHILL-DAVIDSON, H. C. (1960). A practice of anæsthesia, 576. Lloyd-Luke (London).

Studies on the clinical and pathological effects of hydroxydione

J. D. ROBERTSON, EDINBURGH

While most previous reports on hydroxydione have confirmed its value as a safe and satisfactory basal anæsthetic many have, at the same time, found it to possess several disadvantages. Of these the most commonly mentioned are the slowness of the induction, with the occasional complaint of a drawing pain in the arm during and the appearance of thrombosis or thrombophlebitis in the region of the vein after the injection. The frequency of the latter has varied widely in different reports, some observing that it occurred exceptionally while others noted an incidence of up to 77.5 per cent. There seems

little doubt that the rapid injection technique of administration described by Stedtfeld and the use of dilute procaine solution as solvent, have gone some way towards reducing these disadvantages.

The present paper describes clinical experiences in a series of 359 patients to whom hydroxydione was administered by various modifications of this technique and an attempt to make an accurate and impartial estimate of the incidence and severity of injection pain and venous irritation in comparison with sodium thiopentone. In addition, a pathological study has been made of sections of human and rabbit veins into which hydroxydione has been injected, as well as some *in vitro* observations on blood and paper chromatographic investigations on its metabolism.

From the experience gained in this study the value of hydroxydione as a basal anæsthetic is confirmed, particularly for long extra-abdominal operations and for elderly and poor-risk patients. Further, it is suggested that, by the rapid injection technique, delayed onset of unconsciousness and injection pain are not serious drawbacks. However, in both the human and animal series, the incidence of venous irritation is a serious objection. Although thrombophlebitis occurred comparatively infrequently, evidence of painless thrombosis in the region of the injected vein was found, by a careful and impartial observer, in one out of every three patients and this was not significantly altered by the several modifications in the method of administration which were employed. It is suggested, therefore, that if the advantages of this type of basal anæsthesia are to be exploited a search for a new anæsthetic steroid compound, rather than for a new method of administration, would seem to be indicated.

Reference

STEDTFELD, G. (1957). *Anæsthetist*, 6, 140.

The tight brain

J. D. WHITBY, NEWCASTLE UPON TYNE

There are four basic causes of a 'tight brain': cerebro-vascular congestion, cerebral œdema, hydrocephalus, and a space occupying intracranial lesion.

The principles of good neurosurgical anæsthesia are well known, but a swollen brain occasionally follows a smooth induction and a

normal intracranial pressure may survive a stormy one. The first may be due to an inconspicuous respiratory depression; the second possibly to an increase in negative inspiratory pressure that concels out the increased positive expiratory pressure.

The T-piece and the one-way valve prevent rebreathing and offer a slight resistance to inspiration with a minimal resistance to expiration. They will not prevent respiratory depression or actively reduce intracranial pressure.

Controlled respiration with a negative phase lowers intraventricular pressure[1], but some consider hyperventilation and the cerebral vaso-constriction that it produces more important than a negative phase[2,3], which, if more than 5cms of H_2O, narrows the bronchial lumen[4] and may cause air trapping: others consider this vaso-constriction potentially dangerous[5,6].

Controlled hypotension also decreases cerebro-vascular congestion, but carries a risk of retractor anæmia and infarction[7,8].

Hypothermia decreases the cerebral blood flow, intraventricular pressure and brain volume, but Rosomoff's figures are for a combination of hypothermia and controlled respiration with a negative phase in dogs[9].

Dehydration can be hypervolæmic or hypovolæmic. The pressure levels at which neurological signs and symptoms appear are critical[10] and methods producing a dramatic clinical improvement may have less effect on operating conditions. Intravenous hypertonic solutions in excess can cause a vascular congestion as troublesome as any original swelling. Hypertonic urea is said to act mainly on brain tissue and produce minimal congestion[11,12].

With the exceptions of sudden respiratory failure during induction and deterioration after ventriculography, fluid aspiration by the surgeon should only be required in cases with internal hydrocephalus or large intracranial cysts, when it is the logical way of reducing the intracranial pressure.

References

[1] RESSEL, G. (1958). *Anæsthesist*, *7*, 33.
[2] BROWN, A. S. (1959). *Anæsthesia*, *14*, 205.
[3] NORRIS, F. H. (1959). Personal communication.
[4] LYNCH, S., LEVY, A. and ELLIS, K. (1959). *Anesthesiology*, *20*, 325.
[5] CLUTTON-BROCK, J. (1957). *Brit. J. Anæsth.*, *29*, 111.
[6] SUGIOKA, K. and DAVIS, D. A. (1960). *Anesthesiology*, *21*, 135.
[7] ASERMAN, D. (1953). *Brit. med. J.*, *1*, 961.
[8] BROWN, A. S. (1954). *Anæsthesia*, *9*, 17.
[9] ROSOMOFF, H. L. and GILBERT, R. (1955). *Amer. J. Physiol.*, *183*, 19.
[10] KETY, S. S., SHENKIN, H. A. and SCHMIDT, C. F. (1948). *J. clin. Invest.*, *27*, 493.
[11] JAVID, M. (1958). *Surg. Clin. N. Amer.*, *38*, 907.
[12] STUBBS, J. and PENNYBACKER, J. (1960). *Lancet*, *1*, 1094.

Numorphan, a new supplement to anaesthesia

M. SWERDLOW, MANCHESTER

Numorphan (14-hydroxydihydromorphinone) was used in one-hundred-and-fifty patients as an adjuvant to thiopentone-nitrous oxide anæsthesia. The patients were undergoing a variety of operations not requiring the use of muscle relaxants. Anæsthesia was induced with a standard dose of sodium thiopentone, and maintained with nitrous oxide and oxygen and supplementary doses of numorphan were given in response to signs of lightening anæsthesia. The results are compared with those obtained in a similar series of patients who received pethidine[1] to supplement anæsthesia.

It was found that numorphan was more potent and had a more prolonged action than pethidine. Anæsthesia was easier to manage in the patients who received numorphan as the analgesic adjuvant; a greater proportion of these patients had a smooth untroubled anæsthetic. The incidence of respiratory depression was higher in the numorphan series, but speed of recovery and incidence of nausea and/or vomiting were more favourable after numorphan.

It is considered that this new analgesic merits more extensive trial as an adjuvant to anæsthesia.

Reference

[1] SWERDLOW, M., BROWN, P. R. and TETLOW, A. (1960). *Anæsthesia*, *15*, 280.

NEW INVENTIONS

Unless expressly stated by the authors no claim to originality or priority is made and items given under this head include modifications to existing apparatus. The Editor regrets that space considerations make it impossible to publish correspondence on this subject

A drip epidural indicator

MASSEY DAWKINS

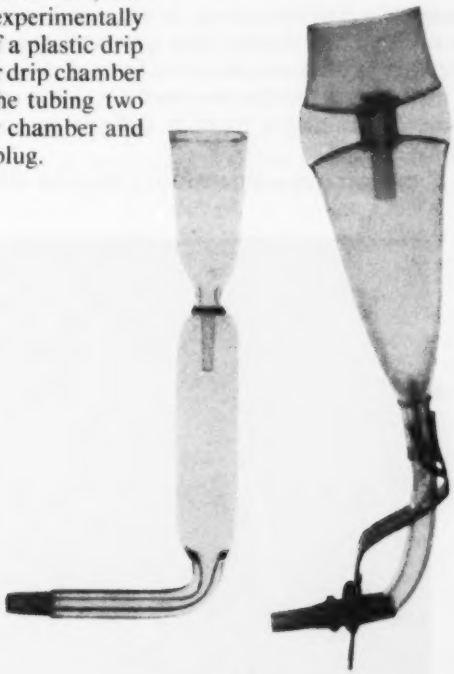
Epidural indicators have in the main, tended to fall into two categories, the tactile and the visual. In the tactile, the sign of loss of resistance to an advancing needle is felt by the thumb resting on the piston of a syringe attached to the needle, or by the discharge of some mechanical device, such as a spring-loaded syringe or needle, or a distended balloon. In the visual, the presence of a negative pressure in the epidural space is indicated by the movement of a drop of saline on the hub of the needle, or of a meniscus in a capillary tube plugged in to the hub.

Attempts have been made to combine these two systems in one device, firstly by Zelenka, who added a distended balloon to the capillary tube, thus giving the meniscus an impulse from behind, and causing the device to function in those 20 per cent of patients who do not possess a negative pressure in the epidural space; and secondly by Brooks, who closed the end of the capillary tube and expanded it into a bulb. If the air in the bulb is heated, it expands and thus provides an impulse behind the meniscus as in the previous device.

But all these indicators are dependent for their efficiency on factors which may be variable. Springs can rust, balloons may perish or leak, heat expanded air may cool and even the tactile sense of the anæsthetist's thumb depends on his physical condition. As far as is known, the force of gravity, which is constant and unvarying, has not been used in an indicator. If an ordinary drip chamber is attached at right angles to a capillary tube, and half filled with sterile saline or the analgesic solution, and plugged into the hub of the advancing needle, then as soon as the epidural space is tapped the drip will commence to flow. It is essential that the drip chamber should only contain just enough air for the drip to function; this can best be achieved by attach-

ing the empty indicator to the epidural needle, and filling the two chambers from below with the analgesic solution by means of a long, fine needle. It is important that a hanging drop is present on the end of the delivery tube, as in some cases only one drop will flow. But if a wide bore needle such as the Tuohy is used, drops are continuous. The system must be kept below 10cm in length, lest its internal pressure exceed that of the cerebro-spinal fluid. If an accidental puncture of the dura mater occurs, then the drip will flow backwards, and the air which was present in the shaft of the needle will appear as a bubble. In my hands this indicator has proved more accurate and reliable than any other, and the incidence of dural puncture is only $1\frac{1}{2}$ per cent, which compares favourably with the average of 4 per cent, compiled from records of over 17,000 cases in the literature.

As shown in the illustration, the device can be made experimentally from discarded parts of a plastic drip set, by cutting the upper drip chamber in half, and severing the tubing two inches below the lower chamber and joining it to the needle plug.



Acknowledgements

I am indebted to my anæsthetic clerk, Mr Michael Watson, for constructing a phosphor bronze strip to stiffen the plastic version, without which, it tends to sag. Problems of opacity on resterilisation can be overcome by drying at 70°C for half-an-hour. I am indebted to Mr D. Ellis for the photograph. The indicator can be obtained from Medical & Industrial Equipment Ltd, 12 New Cavendish Street, London W1.

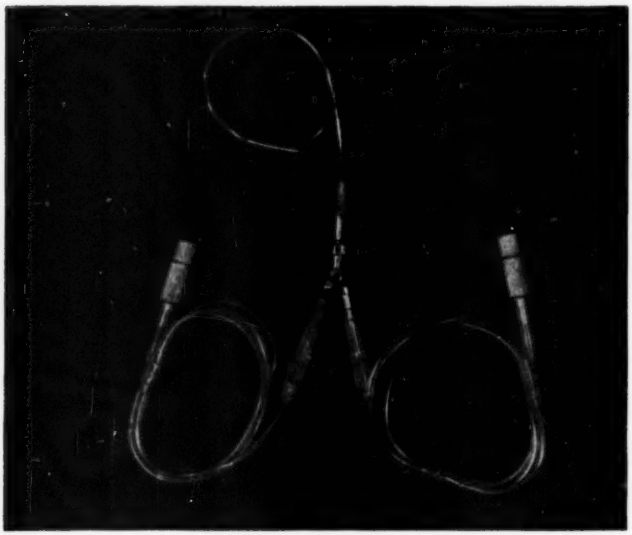
An apparatus for intravenous anæsthesia in the neonate

W. J. THOMSON

The apparatus shown in the photograph, has been designed to simplify the intermittent administration of suxamethonium during nitrous oxide–oxygen anæsthesia in the neonate.

Current techniques[1] involve the injection of suxamethonium into a drip, either directly or via a three-way tap. If direct injection is used, excessive quantities of fluid may be transfused in order to carry the drug into the patient. A three-way tap eliminates this disadvantage, but in these tiny patients, access to it involves disturbance of the towels, thus endangering the sterility of the surgical field. Such conditions make it difficult to see the exact dosage injected from the syringe. In addition, blood often drips reluctantly through the narrow cannulæ required in neonates and some form of pressure is required. When it is remembered that the anæsthetist is also in control of the respiration, these disadvantages make it difficult to handle such a technique single-handed.

The apparatus consists of (*a*) a nylon intravenous catheter with



The assembled apparatus
(The tubes are coiled for convenience of photography)

Luer end: (*b*) a Y-piece made from two wide-bore needles soldered into a Record-Luer adaptor: (*c*) two poly-vinyl connecting-pieces with male and female Luer ends: and (*d*) two Heller one-way valves.

In use, the catheter is suitably inserted into the saphenous vein at the ankle and the apparatus connected up, one connecting-piece previously filled with dilute suxamethonium (5mg/ml) and the other with blood or saline. The Heller valves are connected to the appropriate syringes and placed beside the infant's head at the top of the table. Blood or suxamethonium can now be injected as required, the only 'dead-space' of the apparatus being the small volume of the intravenous catheter (0.1–0.2mls). Resistance to the injection of blood is fairly high, but no appreciable hæmolysis is produced.

Post-operatively the Y-piece and connecting pieces are removed and a Heller valve placed in the intravenous catheter. There is thus retained, for post-operative intravenous therapy, a convenient route which can be kept open for several days, the only limiting factor being a sterile thrombosis of the vein.

Acknowledgements

I am indebted to Mr J. Devlin of the Royal Hospital for Sick Children, Glasgow for the photograph and to Dr W. Auld and Dr H. H. Pinkerton for their help and encouragement.

Reference

[1] HELLINGS, P. M., COPE, R. W. and HAWKSLEY, M. (1958). *Lancet*, *2*, 182.

Note

The nylon intravenous catheters are obtainable from Portland Plastics Ltd: the connecting-pieces (No R.33) from Baxter Laboratories Inc. and the Heller valves from Medical Industrial Equipment Ltd.

Anæsthetic literature

APPARATUS

Simple method for the measurement of alveolar carbon dioxide. STEIN, M. and COLP, C. R. (1960) *J. Amer. med. Ass.*, *173*, 671 (June 11). 11 refs.

A new mask for delivering oxygen and other gases. CATTERALL, M. (1960) *Brit. med. J.*, *1*, 1941 (June 25).

Improved material for Radcliffe tracheostomy tube. SALT, R. H., PARKHOUSE, J. and SIMPSON, B. R. (1960) *Lancet*, *2*, 407 (August 20). 11 refs.

A new method of oxygen determination. BRACKEN, A., GLOVER, J. H. and LONGMUIR, I. S. (1960) *Lancet*, *2*, 411 (August 20).

Resuscitation apparatus. SYKES, M. K. (1960) *Brit. med. J.*, *2*, 596 (August 20).

A new face mask. GARDNER, E. K. and ROCHFORD, J. D. (1960) *Brit. med. J.*, *2*, 383 (July 30). For edentulous patients.

The Cardiff inflating bellows. HILLARD, E. K. and MUSHIN, W. W. (1960) *Brit. med. J.*, *2*, 729 (September 3).

Adaptors for pædiatric anæsthesia and resuscitation. LEVIN, J. (1960) *Lancet*, *2*, 80 (July 9).

Device for supporting Boyle-Davis gag during pharyngeal operations. THOMAS, D. B. and WALTER, F. H. (1960) *Lancet*, *2*, 188 (July 23).

Audio-monitoring of electroencephalography during surgery and anæsthesia. PAMPIGLIONE, G. and PICTON-ROBINSON, N. (1960) *Lancet*, *2*, 352 (August 13).

A warning device for use in surgery. TROTMAN, R. E. (1960) *Lancet*, *2*, 471 (August 27).

An electronic neonatal respiratory monitor. EDGE, W. E. B. (1960) *Lancet*, *1*, 1330 (June 18).

Guide for pudendal nerve block. EATON, E. R. and FLANAGAN, M. B. (1960) *Lancet*, *1*, 1392 (June 25).

ARTICLES OF GENERAL INTEREST

Problems related to open heart operations on children. Part 2. SMITH, R. and ENGINEER, E. H. (1960) *Anæsth. & Analg.*, *39*, 267 (May–June). 8 refs.

Some aspects of anæsthesia for head and neck surgery. NOBLE, A. B. (1960) *Canad. Anæsth. Soc. J.*, *7*, 269 (July). 19 refs.

Reflections on specialization in medicine. LORD COHEN OF BIRKENHEAD (1960) *Ann. Roy. Coll. Surg.*, *27*, 1 (July). No refs.

Statistics in medicine. ARMITAGE, P. (1960) *Ann. Roy. Coll. Surg.*, *27*, 45 (July). 5 refs.

The concentration of anæsthetics in closed circuits with special reference to halothane. (3 articles.) MAPLESON, W. W., GALLOON, S. and MUSHIN, W. W. (1960) *Brit. J. Anæsth.*, *32*, 298, 310, 324 (July). Many refs.

The discovery and pharmacology of cyclopropane. LUCAS, G. H. W. (1960) *Canad. Anæsth. Soc. J.*, *7*, 237 (July). 12 refs.

COMPLICATIONS OF ANÆSTHESIA AND OPERATION

Thermal decomposition of ether in the infant incubator. MENDENHALL, M. K., JENICEK, J. A. and BRYANT, J. M. (1960) *J. Amer. med. Ass.*, *173*, 651 (June 11). 7 refs.

Muscle pains that follow administration of suxamethonium. FOSTER, C. A. (1960) *Brit. med. J.*, *2*, 24 (July 2). 8 refs.

Post-operative vomiting. RIDING, J. E. (1960) *Proc. Roy. Soc. Med.*, *53*, 671 (August). 25 refs. Numerous contributors to this discussion.

Why thiopentone injected into an artery may cause gangrene. BURN, J. H. (1960) *Brit. med. J.*, *2*, 414 (August 6). 13 refs.

Blood loss in gynæcological operations. LOUDON, J. D. O. and SCOTT, D. B. (1960) *J. Obstet. Gynæc. Brit. Emp.*, *67*, 561 (August). 2 refs.

Comparison of post-operative pain and stiffness after the use of suxamethonium and suxethonium compounds. PARBROOK, G. D. and PIERCE, G. F. M. (1960) *Brit. med. J.*, *2*, 579 (August 20). 7 refs.

Cardiac arrest from potassium given in blood transfusions. (1960) *Brit. med. J.*, *2*, 586 (August 20). 8 refs. Leading article.

Hæmorrhage and transfusion as the major cause of cardiac arrest. LEVEEN, H. H. *et al.* (1960) *J. Amer. med. Ass.*, *173*, 770 (June 18). 18 refs.

Profound acidosis in an anesthetised human: report of a case. SCHULTZ, E. A., BUCKLEY, J. J., OSWALD, A. J. and VAN BERGEN, F. H. (1960) *Anesthesiology*, *21*, 285 (May). 46 refs.

Current theories of shock. HERSHEY, S. G. (1960) *Anesthesiology*, *21*, 303 (May). 106 refs.

Circulatory responses to endotracheal intubation in light general anesthesia – the effect of atropine and phentolamine. DE VAULT, M., GREIFENSTEIN, F. E. and HARRIS, L. C. (1960) *Anesthesiology*, *21*, 360 (July). 11 refs.

Incidence and prevention of muscle pain following the administration of succinylcholine. LAMOREAUX, L. F. and URBACH, K. F. (1960) *Anesthesiology*, *21*, 394 (July). 8 refs.

GENERAL ANÆSTHETIC PROCEDURES

Anæsthesia for mass casualties. STEPHENS, K. F. and BOURNE, J. G. (1960) *Lancet*, *2*, 481 (August 27). Single dose cyclopropane.

A clinical comparison of chloroform and halothane by a blind study technique. BAMFORTH, B. J., SIEBECKER, K. L., STEINHAUS, J. E. and ORTH, O. S. (1960) *Anesthesiology*, *21*, 273 (May). 14 refs.

Factors affecting the rapidity of alteration of nitrous oxide concentration in a circle system. EGER, E. I. (1960) *Anesthesiology*, *21*, 348 (July). 32 refs.

Experiences with cardiac catherization using halothane-compressed-air anesthesia. NORTON, M. L. and KUBOTA, Y. (1960) *Anesthesiology*, *21*, 374 (July). 14 refs.

Intramuscular pentothal sodium as an aid to pediatric anæsthesia. DHRUVA, A. J. (1960) *Anæsth. & Analg.*, *39*, 236 (May–June). 1 ref.

Clinical experiences with 1,1,1 trichloroethane. DORNITTE, W. H. and JONES, J. P. (1960) *Anæsth. & Analg.*, *39*, 249 (May–June). 2 refs.

Intravenous non-barbiturate, non-narcotic analgesics. Preliminary studies 1 Cyclohexylamines. COLLINS, V. J., GOROSPE, C. A. and ROVENSTINE, E. A (1960) *Anæsth. & Analg.*, *39*, 302 (May–June). 3 refs.

A study of chloroform anæsthesia in a precision system. 1. The effect on the anion-cation balance in man. DOBKIN, A. B., JOHNSTON, H. J. and SKINNER, L. C. (1960) *Canad. Anæsth. Soc. J.*, *7*, 257 (July). 11 refs.

HYPOTHERMIA

Craniotomy under conditions of quinidine-protected cardioplegia and profound hypothermia. WOODHALL, B., SEALY, W. C., HALL, K. D. and FLOYD, W. L. (1960) *Ann. Surg.*, *152*, 37 (July). 48 refs.

Hypothermia and the heart-lung machine. ROSS, D. H. (1960) *Brit. med. J.*, *2*, 571 (August 20). 4 refs.

Beneficial effects of hypothermia after cardiac arrest. FELDMAN, E., RUBIN, B. and SURKS, S. N. (1960) *J. Amer. med. Ass.*, *173*, 499 (June 4). 15 refs. Report of a case.

Effects of vagal blockade on respiratory work in the hypothermic animal. HALL, F. G. and SALZANO, J. (1960) *Anesthesiology*, *21*, 281 (May 8). 8 refs.

Some effects of inadvertent hypothermia in infant neuro-surgery. HACKETT, P. R. and CROSBY, R. M. N. (1960) *Anesthesiology*, *21*, 356 (July). 10 refs.

Halothane and circulatory occlusion: some experimental and clinical observations. STIRLING, G. R., MORRIS, K. N., ORTON, R. H., BOAKE, W. C., RACE, D. R., KINROSS, F., THOMSON, J. W. and CROSBY, W. (1960) *Brit. J. Anæsth.*, *32*, 262 (June). 12 refs. (Previous work suggesting that halothane prolonged the survival of a brain deprived of its blood supply has *not* been confirmed.)

HYPOTENSION

A study of hypotensive anæsthesia in the elderly. ROLLASON, W. N. (1960) *Brit. J. Anæsth.*, *32*, 276 (June). 10 refs.

Is it safe to employ hypotensive anæsthesia in the elderly. ROLLASON, W. N. (1960) *Brit. J. Anæsth.*, *32*, 286 (June). 45 refs.

LOCAL ANALGESIC PROCEDURES

Brachial plexus anæsthesia – an aid to the casualty surgeon. FOX, M. and BUNTING, D. H. (1960) *Brit. J. Surg.*, *48*, 58 (July). 7 refs. Description and results of 252 cases.

A local anæsthetic solution with longer action. LODER, R. E. (1960) *Lancet*, *2*, 346 (August 13).

Effect of epinephrine upon the duration of spinal anesthesia. EGBERT, L. D. and DEAS, T. C. (1960) *Anesthesiology*, *21*, 345 (July). 8 refs.

A laboratory and clinical evaluation of mepivacaine (carbocaine). GORDON, R. A., KERR, J. H. and TAYLOR, R. (1960) *Canad. Anæsth. Soc. J.*, *7*, 290 (July). 4 refs.

OBSTETRICAL ANÆSTHESIA AND ANALGESIA

Obstetric analgesia based on pethidine-antagonist mixtures. BULLOUGH, J. (1960) *Proc. Roy. Soc. Med.*, *53*, 509 (July). 14 refs.

A clinical appraisal of 2-chloroprocaine in continuous caudal obstrical anæsthesia. NELLERMOE, C. W. *et al.* (1960) *Anesthesiology*, *21*, 269 (May). 6 refs.

Discussion on hypnosis in obstetrics and gynæcology. (1960) *Proc. Roy. Soc. Med.*, *53*, 455 (June).

The effect of pain relief for labour and delivery on the fœtus and newborn. JAMES, L. S. (1960) *Anesthesiology*, *21*, 405 (July). 144 refs.

The routine use of lumbar epidural anæsthesia in obstetrics: a clinical review of 9,532 cases. EISEN, S. M., ROSEN, N., WINESANKER, H., HELLMAN, K., AXELROD, H. I., ROTENBERG, M., RELLE, A. and SHEFFMAN, E. (1960) *Canad. Anæsth. Soc. J.*, *7*, 280 (July). 11 refs.

PHYSIOLOGY AND PHARMACOLOGY

Cultured human respiratory epithelium: its use in the comparison of the cytotoxic properties of local anæsthetics. CORSSEN, G. and ALLEN, C. R. (1960) *Anesthesiology*, *21*, 237 (May). 25 refs.

Effect of respiration, asphyxia and muscle relaxants on cardiac output in the dog. OPDYKE, D. F., CANNILLA, J. E. and BORSUK, G. M. (1960) *Anesthesiology*, *21*, 244 (May). 10 refs.

Experimental hypoxia in dogs. ARGENT, D. E. (1960) *Proc. Roy. Soc. Med.*, *53*, 681 (August). 4 refs.

Neuropathological findings in experimental hypoxia. BUXTON, P. H. (1960) *Proc. Roy. Soc. Med.*, *53*, 683 (August).

A quantitative study of d-tubocurarine in man during diethyl ether analgesia. TIERS, F. M. and ARTUSIO, J. F. (1960) *Anesthesiology*, *21*, 256 (May). 5 refs.

The antisialogogue effect of phenothiazine derivatives: comparison of promaine, levomepromazine, trifluoperazine, prochlorperazine, methdilazine and prothipendyl. DOBKIN, A. B. and PALKO, D. (1960) *Anesthesiology*, *21*, 260 (May). 5 refs.

The influence of anesthetic technique on oxygen consumption during total cardiopulmonary bypass. UNDERWOOD, R. J., ROTH, J. C. and STARR, A. (1960) *Anesthesiology*, *21*, 263 (May). 9 refs.

Potentiation of thiopental anesthesia by derivatives and analogues of phenothiazine. DOBKIN, A. B. (1960) *Anesthesiology*, *21*, 292 (May). 32 refs.

Catechol amine levels during light and deep anesthesia. HAMELBERG, W., SPROUSE, J. H., MAHAFFEY, J. E. and RICHARDSON, J. A. (1960) *Anesthesiology*, *21*, 297 (May). 15 refs.

Effect of phenylephrine on survival and acid-base balance in dogs with acute hæmorrhagic hypotension. LOEHNING, R. W., UEDA, I. and CZORNY, V. P. (1960) *Anesthesiology*, *21*, 363 (July). 10 refs.

Comparison of effects of phenazocine and meperidine on respiration. GREISHEIMER, E. M., KRUMPERMAN, L. W., RUSY, B. F. and ELLIS, D. W. (1960) *Anesthesiology*, *21*, 370 (July). 8 refs.

Cyclopropane anesthesia. III. Effects of cyclopropane on respiration and circulation in normal man. JONES, R. E. *et al.* (1960) *Anesthesiology*, *21*, 380 (July). 24 refs.

Relative respiratory depressant effects of oxymorphone (numorphan) and morphine. BELLVILLE, J. W. *et al.* (1960) *Anesthesiology*, *21*, 397 (July). 14 refs.

Effect of intravenously administered succinylcholine upon cardiac rate and rhythm. BARRETO, R. S. (1960) *Anesthesiology*, *21*, 401 (July). 6 refs.

The action of succinyl choline on the peripheral blood vessels of the cat. WOHLIN, A. (1960) *Acta Anæsth. Scandinav.*, *4*, 21. 22 refs.

A preliminary study of glutethimide (doriden) injectable. SMITH, B., MCDERMOTT, T. F. and KOPPANYI, T. (1960) *Anæsth. & Analg.*, *39*, 240 (May–June). 9 refs. (It was unsatisfactory on several counts.)

Myocardial excitability of dogs during cyclopropane anæsthesia: effect of diffusion respiration. GRAFF, T. D., HARRIS, L. C., ARBEGAST, N. R. and PHILLIPS, O. C. (1960) *Anæsth. & Analg.*, *39*, 293 (May–June). 32 refs. (A ten fold increase in irritability results from the retained carbon dioxide.)

Ferritin and antiferritin serum in irreversible shock. ROTHSTEIN, D. A., ROSEN, S., MANKOWITZ, A. and FULLER, J. B. (1960) *Amer. J. Physiol.*, *198*, 844 (May). 18 refs.

Effect of guanidine on neuromuscular transmission. OTSUKA, M. and ENDO, M. (1960) *J. Pharmacol.*, *128*, 273 (March). 26 refs.

Comparative effect of acidosis induced by acid infusion and CO_2 accumulation. LIGON, J. C. and NAHAS, G. G. (1960) *Amer. J. Physiol., 198*, 1201 (June). 14 refs.

Ventricular fibrillation during uniform myocardial anoxia due to asphyxia. COFFMAN, J. D. and GREGG, D. E. (1960) *Amer. J. Physiol., 198*, 955 (May). 16 refs.

A characterization of the stimulation of mammalian muscle spindles by succinyl choline. BRINLING, J. C. and SMITH, C. M. (1960) *J. Pharmacol., 129*, 56 (May). 11 refs.

Effect of drugs on the fœtus. BAKER, J. B. E. (1960) *Pharmacol. Rev., 12*, 37 (March). 354 refs.

The response of the newborn baby to inflation of the lungs. CROSS, K. W., KLAUS, M., TOOLEY, W. H. and WEISSER, K. (1960) *J. Physiol., 151*, 551 (June). 24 refs. (The response is an apnœa.)

The contribution of the human intercostal muscles to the effort of respiration in man. TAYLOR, A. (1960) *J. Physiol., 151*, 390 (May). 19 refs.

The relative potencies of methohexital and thiopental. BELLVILLE, J. W., FENNEL, P. J., MURPHY, T. and HOWLAND, W. S. (1960) *J. Pharmacol., 129*, 108 (May). 8 refs.

Clinical pharmacology of analgesics: a method of assaying analgesic effect. HONDE, R. W., WALLENSTEIN, S. L. and ROGERS, A. (1960) *Clin. Pharmacol. & Therap., 1*, 163 (March–April). 10 refs.

The pharmacology of neuromuscular blocking agents in man. FOLDES, F. F. (1960) *Clin. Pharmacol. & Therap., 1*, 345 (May–June). 410 refs.

The influence of thiopentone anæsthesia on the blood lipid and blood sugar level. FODOR, J. and GRAFNETER, D. (1960) *Brit. J. Pharmacol., 15*, 282 (June). 10 refs.

The effects of anæsthetics on the cardiovascular system. A review. DOBKIN, A. B. (1960) *Canad. Anæsth. Soc. J., 7*, 317 (July). 82 refs.

Disappearance of various drugs from the cerebrospinal fluid. MAYER, S. E., MAICKEL, R. P. and BRODIE, B. B. (1960) *J. Pharmacol., 128*, 41 (January). 7 refs.

The usefulness of clinical signs for the comparison of intravenous anæsthetics in dogs. MAYNERT, E. W. (1960) *J. Pharmacol., 128*, 182 (February). 16 refs. (Redistribution rather than localisation in fat determines recovery from thiopentone.)

RESUSCITATION

A clinical survey of blood transfusion. GRAHAM-STEWART, C. W. (1960) *Lancet, 2*, 421 (August 20). 15 refs.

Anoxia in the newborn. (1960) *Lancet, 2*, 419 (August 20). Annotation.

Manikin for training in expired-air resuscitation. RUBEN, H. (1960) *Brit. med. J., 2*, 463 (August 6).

A method of controlled oxygen administration which reduces the risk of carbon-dioxide retention. CAMPBELL, E. J. M. (1960) *Lancet, 2*, 12 (July 2).

Fluid replacement in shock and hæmorrhage. HOWARD, J. M. (1960) *J. Amer. med. Ass., 173*, 516 (June 4). 7 refs.

The effect of intragastric oxygen on the oxygenation of arterial and portal blood in hypoxic animals. COXON, R. V. (1960) *Lancet, 1*, 1315 (June 18). 14 refs.

The recovery room: a clinical laboratory. HOWLAND, W. S., SCHWEIZER, O. and BELLVILLE, J. W. (1960) *Anesthesiology, 21*, 251 (May). 9 refs.

TREATMENT AND MEDICATION

Clinical experiences in the treatment of tetanus. ALTEMEIER, W. A., CULBERTSON, W. R. and GONZALES, L. L. (1960) *Arch. Surg.*, *80*, 977 (June). 14 refs.

Dehydration therapy in cerebral hypoxia. COPE, D. H. P. (1960) *Proc. Roy. Soc. Med.*, *53*, 678 (August). 11 refs.

Pre-anesthetic medication without narcotics. WALLACE, G. (1960) *J. Amer. med. Ass.*, *173*, 797 (June 18). 15 refs. Use of promethazine and a sympathomimetic agent in 5,500 patients.

The pharmacologic basis of the treatment of myasthenia gravis. SCHWAB, R. (1960) *Clin. Pharmacol. & Therap.*, *1*, 319 (May–June). 37 refs.

Book Reviews

ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY

ALBERT FAULCONER and REGINALD G. BICKFORD

Pp. viii+90. Figs 35. Charles C. Thomas, Springfield, USA and in British Commonwealth, Blackwell Scientific Publications Ltd, Oxford. Price 38s.

This book brings together, for the first time, all the available knowledge of a difficult subject. Some anæsthetists seem to think that an EEG tracing is a quick and certain way of determining the level of anæsthesia at any given time. The authors' opinion, is, that 'the EEG alone, is no more valid a criterion of depth than is the manifest change of any single physiological system, such as the oculomotor, the respiratory or the cardiovascular system'. This cautious approach is evident throughout the book and extravagant claims are rightly discounted.

There is a good chapter on instrumentation, and graphs showing the EEG levels of narcosis, with the usual agents, are given, but it is clear that many variations occur and that interpretation is difficult. The section on servoanæsthesia is interesting, the principle depending on the fact, that, the electrical output of the brain decreases progressively as narcosis becomes deeper. It is, thus, possible by suitable electronic apparatus, to convert the output of brain potential into corresponding dosage of volatile or intravenous anæsthetic. Servo apparatus has proved to be practicable and can be compared to an automatic pilot on an aircraft. There are, however, many possible factors causing interference and in the human subject an anæsthetist must always supervise the administration. At the same time, it is possible to produce a very steady plane of narcosis for an almost indefinite period by this method. The reader is left with the impression that in the present state of our knowledge the EEG is more useful in the laboratory and for research, than as a monitoring system in practical anæsthesia, except in special cases.

The book is No 395 of the 'American Lecture Series' and is very well produced. There is no index, but a list of ninety-five references is included.

THE PHARMACOLOGY OF ANESTHETIC DRUGS

JOHN ADRIANI

Pp. xvi+232. Fourth edition. Charles C. Thomas, Springfield, USA and in British Commonwealth, Blackwell Scientific Publications Ltd, Oxford. Price 88s.

It is good to see an up-to-date edition of this well-known book, which was first published twenty years ago.

The lay-out remains the same, with large pages summarising the various actions of each drug with tables, figures and diagrams. The result is not a readable textbook, but a mine of reliable information arranged for rapid reference. On superficial examination, most of the recent work on new drugs and methods seems to be covered adequately. A useful glossary of technical terms is included, as well as lists of references under subject headings and a really comprehensive index of twenty-seven pages.

brief duration
with
rapid recovery . . .

'BRIETAL SODIUM'

TRADE MARK

METHOHEXITAL SODIUM

BRAND

A new intravenous barbiturate for induction of anaesthesia in operative procedures of short duration. Recovery is exceptionally rapid, clear-headed and safe. Aqueous solutions are highly stable.

'Brietal Sodium' is supplied in ampoules each containing 0.5 Gm. The average dose is 50–100mg. in a 1% solution.

Full particulars will be forwarded on request.

Lilly

ELI LILLY AND COMPANY LIMITED · BASINGSTOKE · ENGLAND

CLINICAL APPLICATIONS OF DIAGNOSTIC AND THERAPEUTIC NERVE BLOCKS

JOHN J. BONICA

Pp. xix + 354. Figs 44. Blackwell Scientific Publications, Oxford. Price 70s.

There can be few people, on either side of the Atlantic, who have had the experience of Dr Bonica in every variety of diagnostic and therapeutic nerve block. In this monograph, he presents the subject as a whole, to all qualified doctors and not specifically to anæsthetists. In order to avoid disappointment, it should be made clear that the text does not contain many detailed accounts of individual techniques, but general principles are dealt with in a masterly fashion. The author has already described many nerve blocks minutely in his previous work 'The Management of Pain'. Patients suffering from an astonishingly wide variety of diseases, of which pain is a dominant factor, can be greatly helped by an appropriate type of regional analgesia and this book can be thoroughly recommended as a guide to the latest knowledge of the subject. The only major deficiency found by the reviewer, was that the most recent British work on subarachnoid block for intractable pain was not described.

The book is No 342 in the 'American Lecture Series' and is very well produced with clear diagrams. It closes with a list of 150 references and a good index.

ILLUSTRATING MEDICINE AND SURGERY

MARGARET C. MCLARTY

Pp. viii + 159. Figs. 178. E. and S. Livingstone Ltd, Edinburgh and London. Price 37s. 6d.

Miss McLarty's name is familiar to most anæsthetists as being that of the talented artist who has illustrated five of the books written by members of the Nuffield Department of Anaesthetics at Oxford. She is a founder-member of the Medical Artist's Association of Great Britain and has done a great deal of pioneer work in the technique of making diagrams and pictures which really do elucidate the text. This book sets out the fundamental principles of medical illustration and describes methods which can be adopted by any intelligent reader with materials which are readily obtainable. It is true, however, that the more advanced techniques are rather beyond the scope of the casual illustrator and are meant for the use of professional artists. As would be expected, the figures and pictures are outstanding, some of them being in full colour. A glossary and index add to the usefulness of a volume which can profitably be studied by every medical author. Sir Robert Macintosh has written a brief foreword.

The following book has also been received:

OXYGÉNOTHERAPIE

LÉON BINET et MADELEINE BOCHET

Pp. 262. Figs. 43. Masson et Cie, Paris. Price 32NF. (Second edition.)

Correspondence

AN UNUSUAL CASE OF POST-ANÆSTHETIC COLLAPSE

The Editor, *Anæsthesia*

Sir,

This case is presented for interest, as being an unusual and alarming episode, after a straightforward minor operation, in an apparently normal child. A tentative diagnosis of extreme vasovagal overactivity has been made, and readers' comments are invited.

A small boy, aged four-and-a-half years, was presented for tonsillectomy and adenoidectomy. Pre-operative examination revealed a normal child, weighing 40lb, with no relevant past history. Premedication consisted of papaveretum 10mg and scopolamine 0.2mg. Induction one hour later, was with thiopentone 150mg. Anæsthesia was maintained on a Boyle-Davis gag, with nitrous oxide, oxygen and ether. Both the induction and maintenance were quite smooth and free from breathholding, coughing, or spasm. The operation lasted ten minutes and the child was sent to the Resuscitation Ward in the semi-prone position. There, the recovery of consciousness was progressive and uneventful. At the end of fifteen minutes, the child had opened his eyes and cried and was then sent back to the ward. On arrival in the ward, his state of consciousness was confirmed and he was returned to bed and kept under observation.

About twenty minutes after his arrival in the ward, he was observed to go very pale suddenly, but there was no coughing or choking episode. The anæsthetist was sent for at once. On his arrival, the child appeared to be 'in extremis', very pale and with a slightly cyanotic mottling of the face. He was lying limply, deeply unconscious with masseters relaxed, and pulse not readily perceptible. After a few moments he took about six gasping breaths with obvious laryngeal stridor, followed by a period of several minutes without respiratory effort. These breaths had the effect of somewhat improving the cyanotic tinge, which, however, returned as soon as the respiratory effort ceased. At the same time, his pulse could be felt beating slowly, but strongly. Artificial respiration with positive-pressure oxygen was then applied and quite easily overcame the laryngeal spasm; the child's colour returned to normal; this was followed shortly after by spontaneous regular respiration. The child was still deeply unconscious, there was some oozing of blood from the mouth and bubbling; and it was decided to bring the child back to the operating theatre for further observation.

At this time, in spite of the evidence that the child's reflexes had fully returned, it was thought that his airway must, in fact, have become obstructed, and that the condition was the result of a prolonged episode of cerebral hypoxia which had passed unobserved. This appeared to be confirmed when the level of unconsciousness progressively lightened over the next half-hour and the child responded to stimuli with movement of the limbs and flickering of the eyelids. It was noted, however, that there was a very marked degree of sinus arrhythmia present.

The oozing from the tonsil bed had ceased, and respiration was proceeding quite steadily and uneventfully, when suddenly the child strained as if to cough,

but did not, in fact, do so. Respiratory effort immediately ceased. He then became very pale with the same slight cyanotic mottling as before. The level of unconsciousness deepened and the child no longer responded to any stimuli.

As before, positive-pressure oxygen from a face-mask brought a flow of colour back to the face, but over the next fifteen minutes the patient only took periodic crowing breaths, accompanied by very marked sinus arrhythmia of about 3:1 (180/min:60/min). Laryngoscopy showed the cords in tight apposition and some stale blood and mucus in the laryngopharynx, removal of which, however, produced no change. It was now considered that there was a marked degree of vasovagal over activity, and on this assumption, atropine 0.3mg was given intravenously, combined with succinylcholine 20mg, to facilitate a thorough toilet of the pharynx.

After three minutes of artificial ventilation, respiration returned at the rate of about 20/min, which soon became normal in volume and remained entirely regular from then on. The pulse rate was recorded at 175/min with no sinus arrhythmia and this steadily dropped during the following half-hour to 120/min. The level of unconsciousness also lightened progressively and without further relapse, so that three-quarters-of-an-hour after the atropine had been given, the child opened his eyes, cried and attempted to sit up. Three hours afterwards, he was sitting up in bed talking brightly to his parents and was, in fact, more wakeful and alert than some of the other cases on the morning's list.

The following day, clinical examination revealed no abnormalities, and as far as could be judged, there was no evidence of any cerebral damage due to hypoxia. X-ray of the chest was normal. ECG recordings showed sinus rhythm, with a minor degree of sinus arrhythmia. There was no significant change on sinus carotid pressure.

The child was discharged from hospital five days after the operation and has remained completely well and symptomless since.

Yours faithfully,
J. M. Haughton,
R.N. Hospital, Bighi, Malta G.C.

BERNARD JOHNSON MEMORIAL

The Editor, *Anæsthesia*

Sir,

An appeal for funds to set up a memorial to Bernard Johnson was launched last March. It was hoped at that time to raise the sum of £6,000, which would cover the cost of a memorial plaque to be placed in the Research Laboratories of the Faculty and to endow the salary of the Faculty Adviser in Postgraduate Studies. To date approximately £3,000 has been raised, which falls some way short of the minimum required for this endowment.

An anonymous donor has most generously offered to match any further donations received before 27th March 1961, when the fund will be closed. Should any of your readers wish to subscribe, or to add to their previous donations, their contributions should be addressed to me at the Faculty of Anæsthetists, Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2.

Yours faithfully,
Geoffrey Organe,
Dean of Faculty

Association News

The Annual Meeting of the Association was held in London at The Royal College of Surgeons on 4th–5th November and was attended by two hundred Fellows and Members.

The Report of Council for 1959–60 was presented and will be circulated later. The following Officers and Members of Council were elected:

PRESIDENT	Dr Ronald Jarman, *London*
VICE-PRESIDENTS	Professor T. Cecil Gray, *Liverpool* Dr V. O. McCormick, *Dublin*
HONORARY TREASURER	Professor E. A. Pask, *Newcastle upon Tyne*
HONORARY SECRETARY	Dr H. J. V. Morton, *London*
EDITOR	Dr C. Langton Hewer, *London*
MEMBERS OF COUNCIL	
Fellows	Dr John Beard, *London* Dr Vernon F. Hall, *London* Dr H. H. Pinkerton, *Glasgow* Dr R. P. W. Shackleton, *Southampton*
Member	Dr E. Elwyn Evans, *Swindon*

The President, in thanking Officers and Members of Council for their support during the past year, paid special tribute to the work undertaken by Dr John Beard as Honorary Secretary during the past four years and by Dr Vernon Hall who had served as Honorary Treasurer since 1955.

Dr E. S. Rowbotham and Dr Harry J. Shields were elected Honorary Fellows.

Dr Stanley Campbell, *Toronto*; Dr Stuart Cullen, *San Francisco* and Dr R. A. Gordon, *Toronto* were elected Corresponding Fellows.

An addition to the Rules to allow for the election of Overseas Associates was approved. Doctors engaged in the practice of the specialty abroad, who have received not less than six months' training in an approved post in Great Britain or Ireland, are now eligible for election as Overseas Associates. They will have no voting rights.

The third John Snow Memorial Lecture was given by Sir Ralph Stevenson. In a paper entitled *From the Mediterranean to the Far East and back* he vividly described some of his many interesting experiences as a diplomatist in Spain, Yugoslavia, China and Egypt during the years 1938–55.

By kind permission of the President and the Council of the Section of Anæsthetics of the Royal Society of Medicine, the meeting of the Section was held at the College during the Association's meeting. Dr Robert M. Smith of Boston, Massachusetts, read a paper on *Anæsthesia for emergency procedures in children.*

The Annual Dinner was attended by 227 Fellows, Members and guests. The toast of the Association was proposed by Sir Arthur Porritt to which the President, Dr Ronald Jarman, replied. Dr Russell Davies proposed the health of the guests and Mr Arthur Bell replied to this toast.

Papers were read at the morning sessions on Friday and Saturday; summaries

of these will be found elsewhere in this issue. A trade exhibition was held throughout the meeting.

The Annual Meeting 1961 will be held in Dublin from 18th–21st October.

A full programme of scientific and social events is being arranged. The latter will include a State Reception and also a visit to the Abbey Theatre at the invitation of Bord Failté (The Irish Tourist Board).

Details of the programme will be available later and Fellows and Members will receive particulars regarding hotel accommodation, etc. from Bord Failté.

Readers are reminded that the Association of Anæsthetists is compiling a **press-cutting book** in order to gather information from the lay press regarding the impact of anæsthesia on contemporary life. Press-cuttings relating to anæsthesia from local or national press, including the name and date of the paper, should be sent to Dr J. B. Wyman, Department of Anæsthesia, Westminster Hospital, SW1.

Some readers may have new information of importance to contribute although, for one reason or another, they feel unable to write a full-length article. The Editorial Board is always pleased to consider short items which might be published under such titles as 'Preliminary Communication', 'Anæsthetic Memoranda' or 'Case Report'. The correspondence columns are, of course, available to those who require advice or opinions from other readers.

Research Prizes 1961. The Association of Anæsthetists of Great Britain and Ireland is offering three prizes annually (£100, £50 and £25) for papers based on research in anæsthesia or related subjects. Entrants need not be members of the Association, but the work described must have been carried out in Great Britain, Ireland or the British Commonwealth. Papers shall not exceed 5,000 words in length and shall be typewritten in English. Three copies of the essay shall be submitted.

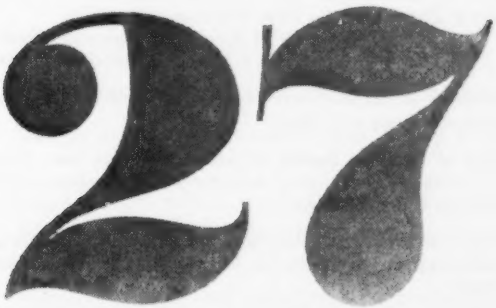
Papers must be original and refer to work which has not previously been published, though an exception to this rule will be made in the case of papers which have been published in '*Anæsthesia*' during the preceding year. Prize winning entries will become the property of the Association. The decision of the Council of the Association of Anæsthetists in all matters relating to the research prizes shall be final.

Essays shall be submitted to the Honorary Secretary of the Association of Anæsthetists of Great Britain and Ireland, 47 Lincoln's Inn Fields, London WC2 on or before 31st March 1961.

The **Section of Anæsthetics of the Royal Society of Medicine** is able to offer a prize of £30 for the best paper written by a medical practitioner of Senior Registrar or Registrar status in the National Health Service holding a clinical appointment in anæsthesia. Fellowship of the Royal Society of Medicine is not necessary for entry. The subject will be of the author's choice, but must be connected with anæsthesia. All papers for the 1962 award must be submitted by 1st January 1962. Further details and rules of the prize can be obtained from the Honorary Secretary, Section of Anæsthetics, Royal Society of Medicine, 1 Wimpole Street, London W1.

The **Section of Anæsthetics of the Manchester Medical Society** has arranged the following programme for 1961, the meetings being held in Staff House of the University at 8 p.m.

focus on anaesthesia



DEVONSHIRE STREET W1

This address is more than a familiar name to anaesthetists the world over. On display are examples of all the anaesthetic apparatus, resuscitation and oxygen therapy equipment and accessories supplied by British Oxygen—of which demonstrations can readily be given. And here is helpful information about the whole British Oxygen medical range. There is also a comprehensive anaesthetic reference library open to all visitors . . . a special display of interesting early equipment . . . facilities for the loan of equipment and lecturing aids for speakers . . . and an experimental workshop actually on the premises. Please call and see us. You are always welcome at no. 27.

THE BRITISH OXYGEN COMPANY LIMITED

MEDICAL DEPARTMENT · 27 DEVONSHIRE STREET · LONDON W.1.
TELEPHONE: WELBECK 2202

THURSDAY 19TH JANUARY	Mr T. B. FitzGerald, Dr J. B. Fawcitt, Dr I. Nisbet, Dr R. I. Mackay. Symposium on 'The management of respiratory failure in pædiatrics'.
THURSDAY 16TH FEBRUARY	Registrars' Meeting Dr J. Greenan, Dr J. B. Montgomery.
THURSDAY 16TH MARCH	Dr F. L. Robertshaw.
THURDSAY 20TH APRIL	Joint Meeting at Liverpool Dr M. Swerdlow, 'Epidural studies'. Dr A. L. Stead, 'Dental anæsthesia for children'.

The **Scottish Society of Anæsthetists** (founded in 1914) has issued a most interesting and informative newsletter of 21 pages.

The **North-East of Scotland Society of Anæsthetists** has been founded by the amalgamation of the Departments of Anæsthesia in Aberdeen and Dundee. The first President is Dr W. N. Rollason.

Dr J. D. Robertson has been appointed **Director of Anæsthetics at the Royal Infirmary, Edinburgh** in succession to Dr John Gillies who retired on 30th September 1960.

primarily peripheral...

...describes the action of 'VASOXINE', the pressor agent which does not increase cardiac output

'Vasoxine' produces a rapid, prolonged, and powerful rise in blood pressure without cardiac or cerebral stimulation. It acts within 1 to 2 minutes after intravenous injection, and about 20 minutes after intramuscular injection, the action being maintained for an hour or more.

Tachycardia is not produced by 'Vasoxine'; rather does it cause bradycardia, thus sparing the heart muscle.

Because of its unique properties it is especially indicated in hypotension after spinal anaesthesia, and in cyclopropane or halothane anaesthetised patients.

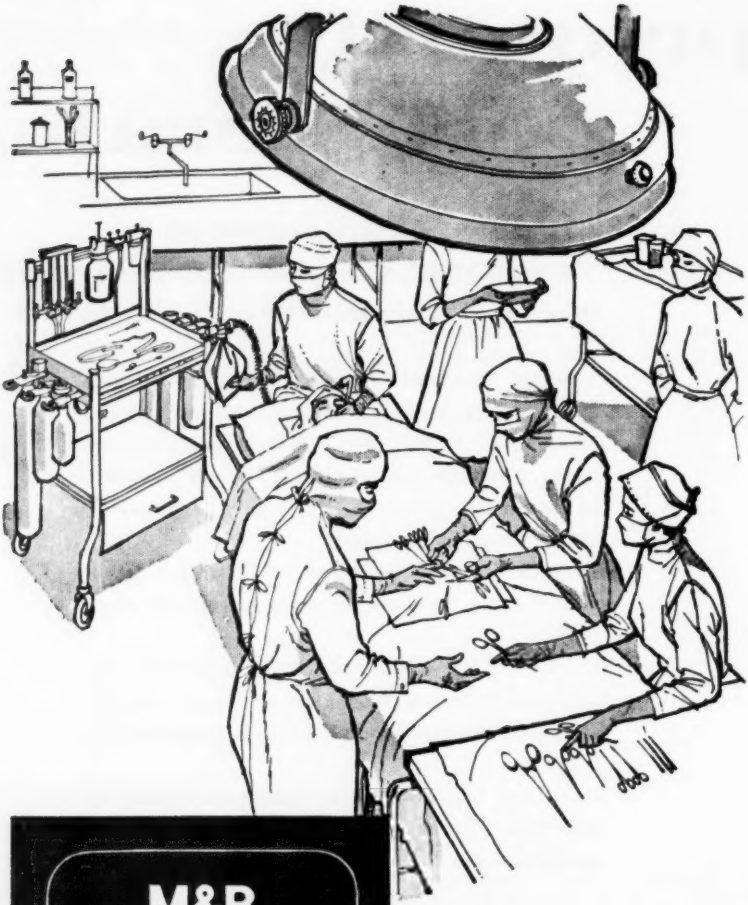
'Vasoxine' is available in boxes of 5 and 25 ampoules of 1 c.c., each containing 20 mgm. methoxamine hydrochloride.

'VASOXINE'

Injection of Methoxamine Hydrochloride

BURROUGHS WELLCOME & CO. LONDON

(The Wellcome Foundation Ltd)



M&B

brand

ANAESTHETIC ETHER B.P.

MANUFACTURED BY
MAY & BAKER LTD · DAGENHAM
Tel: DOMinion 3060 Ext: 317

Renowned for its reliability and consistent high quality. Supplied in containers especially designed for ease of handling.

Detailed information is available on request.

PHA 1213

Faculty News

The Thirteenth Anniversary of the Faculty will be celebrated on Wednesday 15th March 1961. The Annual Meeting will be at 3 pm and Dr R. P. W. Shackleton, FFARCS will deliver the Frederic Hewitt Lecture at 4 pm. The Anniversary Dinner will be held at 7.45 pm. Further details will be circulated to all Fellows and Members.

Intensive Courses. During 1961 the Faculty will be arranging only two courses of lectures, demonstrations and tutorial discussions. These will be 10th–21st April and 9th–20th October.

FFARCS. The following candidates were successful at the examination held in July :

Wakely, Denis
Whittard, Brian Ralph
Hutton, Donald Stuart
Bishop, Cecil
Jackson, David Cowan
Relton, John Eric Sparks
Atherley, Derek Walter
Taylor, Gordon James
Murray, Brian Robert Pairman
Utting, John Edward
Jordan-Sikorska, Zbigniewa
Maciejewski, Andrzej
Dunkin, Laurence Joseph Francis Xavier
Lamont, Archibald Stewart McCallum
Cox, James
D'Souza, Peter Bruno
Hardeman, Maureen Elisabeth
Smith, Keith Glennie
Badola, Raghubar Prasad
Barrow, Michael Edwin Haynes
Howells, Thomas Hillary
McGowan, Stuart Watson
Ward, Cyril
Webb, Selwyn James Smith
Yeung, Ming-Hon
Baldasera, Joseph
Bennetts, Frank Edwin
Browne, Ronald Austin
Bush, Gordon Henry
Emery, Eric Roy John
Hutchinson, Ruth
Munro, Thomas Norman
Paterson, Ian Sillars
Pledger, Herbert Gordon
Sandison, John Westwood
Alexander, John Pentland
Doctor, Noormohmed Haji Ahmed
Hui, Sylvia Lock Seung
Kinnell, John Dunford
Lewis, Raymond Neville
McNeil, William Townley
Robbie, Douglas Stewart
Spencer, Geoffrey Tallent
Whitwam, James Gordon
Crew, Alan David
Larard, David Geoffrey
Peeling, Audrey Margaret

Faculty of Anaesthetists, Royal College of Surgeons in Ireland

At the Board of the Faculty Meeting held in November, the presentation by the Dean of the Faculty of Anæsthetists of the Royal College of Surgeons of England, of an illuminated scroll bearing the good wishes and felicitations of the English Faculty, together with Sir Zachary Cope's *History of the Royal College of Surgeons of England*, with an artistic dedication to commemorate the inauguration of the Irish Faculty, was acknowledged with gratitude. The Registrar of the College was requested that the scroll and book be given an honoured place in the archives of the College.

A further list of names was approved for submission to the Council for admission to Fellowship in the Faculty. It is hoped to arrange a date in February for the formal admission of the new Fellows.

Regulations for the FFARCSI examination were formulated and are being forwarded to the Council for consideration and approval. It is hoped to hold the Primary examination in June 1961.

Commonwealth and Foreign News

The Sixth Postgraduate Course in Anesthesiology sponsored by the Division of Anesthesiology and the Postgraduate Medicine Division of the **University of Utah,** is scheduled to be held 6th–9th February 1961 at the New World Motor Hotel, adjacent to the Salt Lake County Hospital. Questions regarding the course should be addressed to the Director of Graduate and Postgraduate Medical Education, College of Medicine, University of Utah, Salt Lake City.

The 49th annual meeting of the **Fédération Dentaire Internationale** will be held from 9th–15th July 1961 in Helsinki. On 10th–11th July papers will be read on local and general anæsthesia in dentistry. Particulars can be obtained from the Organising Committee Domus Academica A, Helsinki, Finland.

There are vacancies for two anæsthetists at the **Christian Medical College and Hospital, Vellore, S. India.** Any interested readers should communicate direct with Dr Gwenda Lewis at the hospital (Post Box No. 3).

The **University of Minnesota** is organising a continuation course in anesthesiology from 6th–8th February 1961 at the Centre for Continuation Study. Particulars can be obtained from the Director, The Medical School, Minneapolis 14.

During 1960 the **New Zealand Society of Anæsthetists** have enjoyed visits from Dr P. Safar of Baltimore, Dr F. F. Foldes of Pittsburgh and Dr R. W. Cope of London.

REVISED SUGGESTIONS TO CONTRIBUTORS

Original articles, 'New Inventions' etc. are accepted for publication on the understanding that they are contributed exclusively to '*Anæsthesia*', and become the property of the Association of Anæsthetists. Articles are subject to such alterations as the editor may deem necessary, but no major alterations will be made without the author's consent. After publication, the editor will be pleased to consider requests by authors to borrow and use any blocks made to illustrate their articles.

PREPARATION OF ARTICLES

Articles should be typewritten on one side of the paper only, and should be double spaced. Margins of 1½" should be left on both sides of the typescript. Corrections should be made in ink, and should be legibly written. The first sheet of the article should contain only the following details: title of the article; the author's name and the higher of his degrees and diplomas; his present or immediate past appointment; the address to which proofs of the article should be sent.

TITLES OF ARTICLES should be restricted to five words. If this is impossible, a subsidiary title of not more than twelve words can be inserted. A more detailed description of the scope of the article can be given in the first paragraph of the text.

HEADINGS IN THE TEXT are useful to 'signpost' the arguments elaborated in the article. They should be brief and clearly defined in the typescript. Main headings should be typed in capitals, and subsidiary headings to these main headings should be typed in small letters and underlined. No heading should appear in the text until after the first or second paragraph. Too many headings are better than too few. The numbering of headings and paragraphs is not recommended.

THE USE OF FIGURES in articles should be watched carefully. Where statistics are given in the text of the article, figures should be used; likewise the measurements of drugs should be given in figures. But phrases such as 'After three days', 'ten minutes later' etc. should be given in words.

DRUG NAMES AND MEASUREMENTS. The established practice is to use the BPC Approved Name for all drugs and not the chemical or trade name. The only exceptions are when a drug has not been named by the BPC in time for publication, and in the case of certain unusual drugs, the trade name may be given in parenthesis after the approved name, *e.g.* hyoscyamine (bellafoline). The dose of drugs etc. should be given in metric quantities, except for those drugs which are commonly prescribed in avoirdupois measures. In the latter case, the metric equivalent should be given in parenthesis.

REFERENCES to the literature should be clearly indicated in the text by superior figures(⁹), and should be set out fully in numerical order on the following system: LANGLEY, J. N. (1919). *J. Physiol., 53, May*, 120. The list of references should form the last sheets of the article.

ILLUSTRATIONS. Line drawings, charts and diagrams should be made in black indian ink on smooth white card, and should be approximately 6½" wide. Reversed drawings (white lines on a black background) are not suitable. Any necessary lettering should be drawn in plain block capitals. Photographs should be strong black and white prints on glossy paper. All important details should be very lightly marked on the back of the print with a soft pencil. This should be done on a hard surface such as a window pane or the glass of an X-ray viewer. The use of ball point and fountain pens, rubber stamps, hard pencils and typewriters on the back of the print cause damage to the photographic emulsion, and show in the reproduction. Likewise, the use of paper clips should be avoided. A typed slip containing the following details should be attached to the back of all illustrations: author's name and title of article; the figure number and the relevant caption. This slip should be attached with strips of self adhesive tape.

CAPTIONS TO ILLUSTRATIONS should be brief, but sufficient to describe the illustration.

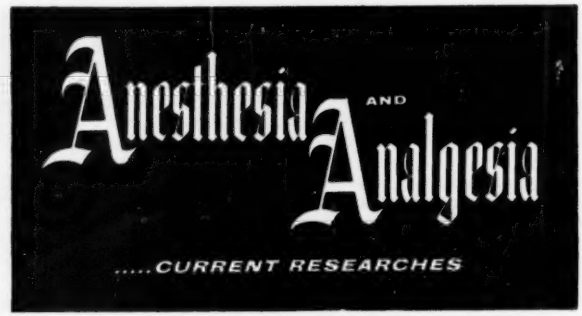
EXCERPTS

Authors of original articles are supplied with fifty copies of their article free of charge. Where there is more than one author, the copies will be sent to the first named author unless other instructions are sent to the publishing office in advance of publication. Excerpts cannot be provided for 'New Inventions' or correspondence, though reprints can.

REPRINTS

Reprints of articles, 'New Inventions' and correspondence can be provided at agreed prices. They should be ordered on the card enclosed with the proofs. Orders should be sent direct to the printers, if possible before publication. Orders for reprints sent in more than three months after publication day cannot be supplied at the agreed prices, and are subject to quotation.

Communications to the printers should be addressed: George Pulman & Sons, 24 Thayer Street, London W 1.



Journal of the International Anesthesia Research Society — Enlarged and Modernized

- 50 to 80 pages of scientific material by leading anesthesiologists, 6 times a year.
- A capsule review of all scientific articles at a glance.
- Strictly Personal—a column of opinion written by anesthesiologists for anesthesiologists.
- News about people you know.
- Biographies and photographs of all the authors.
- Color printing and cartoons, for easier readability.
- A review of new drugs and equipment.
- Office hints, material for your secretary, book reviews.
- Comprehensive biographies of the leaders in anesthesiology.
- Letters and opinions in the editor's special column.

International Anesthesia Research Society and Anesthesia and Analgesia - - - Current Researches

Membership Application and Subscription Blank

A. William Friend, M.D., Executive Secretary ..... 19.....
Wade Park Manor, Cleveland 6, Ohio, U.S.A.

I enclose my check ( ) money order ( ) for $15.00. Enter my Membership for the Society ( ) and Subscription to Journal ( ).

Name..... Degree.....

Street.....

City..... State..... Country.....

GENERAL HOSPITAL
ST. JOHN'S, NEWFOUNDLAND, CANADA

RESIDENTS IN ANAESTHESIA

Applications are invited to fill vacancies in Anaesthesia on the Resident Staff of the General Hospital, St. John's, Newfoundland. This 456-bed acute general hospital has all major services except Obstetrics.
These training positions are recognized and approved by the Royal College of Physicians and Surgeons of Canada, as well as the Faculty of Anaesthetists, Royal College of Surgeons of England. Salary range is $3,600.00 - $6,000.00 (£1,309-£2,181) per year, depending on previous training and experience. An additional allowance of $50.00 (£18) monthly is payable to successful applicants with one or more dependants who reside in St. John's. Board and lodging can be provided in the hospital at a cost of $55.00 (£20) per month. Transportation is provided from Canadian and United Kingdom centres on the basis of one year's service. Further information can be obtained from The Superintendent, The General Hospital, St. John's, Newfoundland, Canada.

EDUCATION & RESEARCH TRUST FUND

The Council of the Association will be pleased to consider applications from Fellows or Members needing financial assistance for educational or research purposes. Applicants for travel grants should state the objects of their proposed visits and submit fully detailed itineraries. Applicants for grants for research should state not only the objects of their investigations but also their proposed methods of experimentation. In all cases applicants should provide evidence that they have been unable to procure any or all of the necessary assistance from local sources. Any apparatus acquired through this fund remains the property of the Association of Anæsthetists and must be made available for the use of other Fellows or Members if subsequently required.

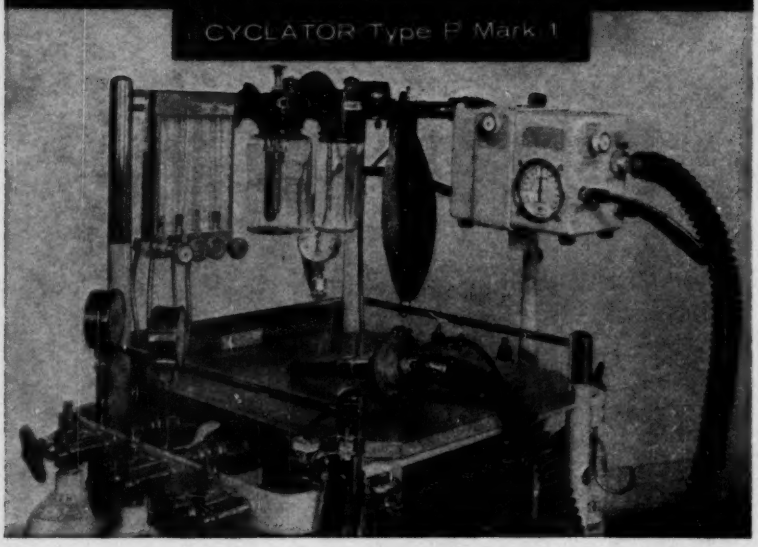
Published by
THE ASSOCIATION OF ANÆSTHETISTS OF GREAT BRITAIN & IRELAND
47 LINCOLN'S INN FIELDS, LONDON WC2, ENGLAND

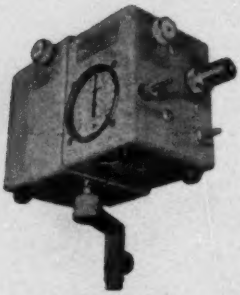
Neither the Editor nor the Association is in any way responsible for the statements made or the views expressed by the Contributors

Printed in Great Britain by George Pulman & Sons Ltd.
24, Thayer Street, London, W.1.

BRITISH OXYGEN

equipment and gases used
daily in the service of medicine





The CYCLATOR Type P Mark I is an intermittent positive pressure lung ventilator of the pressure cycling controller type. It is intended mainly for use on the open circuit of a Boyle type anaesthetic apparatus for automatic controlled respiration.

Controls are provided permitting variation of lung inflation pressure up to 35 cms. H_2O, and expiratory time between $\frac{1}{2}$ second and 30 seconds.

FOR DETAILED INFORMATION PLEASE GET IN TOUCH WITH:

THE BRITISH OXYGEN COMPANY LIMITED
MEDICAL DEPARTMENT, SPENCER HOUSE, 27 ST. JAMES'S PLACE, LONDON, S.W.1